IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/478,262 Confirmation No. 2549
Applicants	:	Evert J. BUNSCHOTEN et al.
Filed	:	May 25, 2004
Title	:	PHARMACEUTICAL COMPOSTION FOR USE
	:	IN HORMON REPLACEMENT THERAPY
Group Art Unit	:	1617
Examiner	:	San Ming R. HUI
Customer No.	:	28289

Application No.	:	10/478,264 Confirmation No. 4962
Applicants	:	Evert J. BUNSCHOTEN et al.
Filed	:	May 25, 2004
Title	:	USE OF ESTROGEN COMPOUNDS TO
	:	INCREASE LIBIDO IN WOMEN
Group Art Unit	:	1617
Examiner	:	San Ming R. HUI
Customer No.	:	28289

Application No.	:	10/478,357 Confirmation No. 3771
Applicants	:	Evert J. BUNSCHOTEN et al.
Filed	:	May 25, 2004
Title	:	DRUG DELIVERY SYSTEM COMPRISING A
	:	A TETRAHYDROXYLATED ESTROGEN FOR
	:	USE IN HORMONAL CONTRACEPTION
Group Art Unit	:	1617
Examiner	:	San Ming R. HUI
Customer No.	:	28289

Application No.	:	10/517,509 Confirmation No. 1291
Applicants	:	Herman J. T. Coelingh Bennink et al.
Filed	:	June 13, 2005
Title	:	METHOD OF TREATING HUMAN SKIN AND
	:	A SKIN CARE COMPOSITION FOR USE IN
	:	SUCH METHOD
Group Art Unit	:	1617
Examiner	:	Samira JEAN-LOUIS
Customer No.	:	28289

DECLARATION

I, Speroff, Leon declare and state the following:

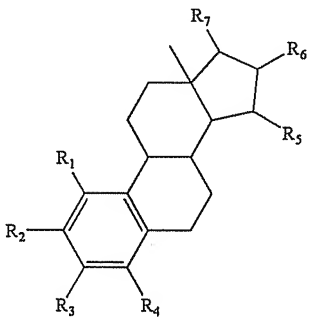
1. A detailed listing of my publications, together with details of my education, are given in my *curriculum vitae* which is attached as Exhibit A.

2. Based on my academic training and professional experience, I consider myself an expert in the field of estrogen-related therapies and treatments, and I was such a person in 2001 and 2002.

3. I have received copies of patent applications that I understand were filed in the United States and correspond to the above-captioned applications.

4. I understand that the above mentioned patent applications relate to:
- new methods of contraception (Appln. 10/478,357);
- new methods of hormone replacement therapy (Appln. No. 10/478,262);
- a new method of increasing female libido (Appln. No. 10/478,264);
- a new method treating vaginal dryness (Appln. No. 10/517,509).

The aforementioned methods have in common that they comprise administration of the following estrogenic component:



wherein R_1, R_2, R_3 and R_4 independently are a hydrogen atom, a hydroxyl group or an alkoxy group with 1-5 carbon atoms. R_5, R_6 and R_7 are hydroxyl groups. No more than three of R_1, R_2, R_3 and R_4 are hydrogen atoms. The invention also includes using variations of this formula, such as precursors capable of liberating a substance according to the aforementioned formula and mixtures of one or more of the aforementioned substances and/or precursors. One embodiment of the aforementioned formula is estetrol.

5. I have also received copies of Office Actions that have been issued in relation to the above referenced pending patent applications. Specifically, I have received copies of the following Office Actions:

OA-1 - 10/478,262 (Non-final Office Action mailed on May 15, 2008)
OA-2 - 10/478,264 (Non-final Office Action mailed on March 6, 2008)
OA-3 - 10/478,357 (Non-final Office Action mailed on May 16, 2008)
OA-4 - 10/517,509 (Non-final Office Action mailed on March 26, 2008)

6. I have further received copies of the following references that I have been told have been cited in the above mentioned Office Actions against the independent claims of the above referenced pending patent applications.

Publications mentioning estetrol:

D1 US 5,211,952 (Spicer et al.) – cited in OA-4

D2 US 5,340,584 (Spicer et al.) – cited in OA-2

D3 US 5,340,586 (Pike et al.) – cited in OA-1, OA-2 and OA-3

D4 US 2004/0192598 (Kragie) – cited in OA-4

D5 Holinka, Biology of Reproduction, 1979; 20(2): 242-246 [1] – cited in OA-1 and OA-2

D6 Holinka, Biology of Reproduction, 1980; 20(4): 913-926 [2] – cited in OA-1 and OA-2

Publications not mentioning estetrol:

E1 Ullom –Minnich, American Family Physician, 1999; 60: 194-202 – cited in OA-1

E2 Katzung, Basic and Clinical Pharmacology, 6th ed., 1995, 608-624 – cited in OA-3

E3 Willhite et al. (Pharmacotherapy, 2001, vol. 21, issue 4, 464-480 – cited in OA-4

E4 Sitruk-Ware et al. (Schweiz. Rundsch., Med. Praxis, 1997, vol. 86, No. 33, 1245-1248 – cited in OA-4

It is my understanding that the independent claims of the pending patent applications that are the subject of this Declaration were rejected as being unpatentable over the above cited references under 35 U.S.C. 103(a) (obviousness). I have been asked to comment on my understanding of the state of the art prior to June 11, 2002, which I understand is the priority date for Appln. No. 10/517,509. Particularly, I have been asked whether, prior to June 11, 2002, a person of ordinary skill in the art would have considered it obvious to use estetrol in the pharmacological applications listed in § 4. More particularly, I have been asked whether, prior to the June 11, 2002, a person of ordinary skill in the art would have been motivated to use estetrol in the pharmacological applications listed in § 4, and whether the discovery that estetrol was pharmacologically useful in these applications is unexpected and surprising.

7. It is my view that, prior to June 11, 2002, for the reasons presented below, a person of ordinary skill in the art would not have expected estetrol to be pharmacologically useable, and that the Applicants were the first to discover the pharmacological usefulness of estetrol. In addition, and more particularly, it is my opinion that, prior to June 11, 2002, a person of ordinary skill in the art would not have expected estetrol to be pharmacologically active when orally administered.

8. I declare that before June 11, 2002 I had no knowledge of any concrete pharmacological application of estetrol. Furthermore, before June 11, 2002, I did not expect that estetrol can be used effectively as a drug in therapeutic treatments or in hormonal contraceptives. Based on the data from scientific literature that was available before June 11, 2002, I would have expected estrogenic activity of estetrol to be too low for pharmacological applications, such as the ones recited in Applicants' claims.

9. My view that a person of ordinary skill in the art would not have expected estetrol to be pharmacologically active is supported by leading textbooks in the field of endocrinology. In "Clinical Gynecologic Endocrinology and Infertility" [3] estetrol is solely mentioned in Chapter

8 (The Endocrinology of Pregnancy) under the subheading "Measurement of Estrogen in Pregnancy" (page 287) and in the index. On page 287 it is stated that "Estetrol (15alpha-hydroxyestriol) is formed from a fetal precursor and is very dependent on 15alpha-hydroxylation activity in the fetal liver. The capacity for 15alpha-hydroxylation of estrogens increases during fetal life, reaching maximum at term. This activity then declines during infancy and is low, absent or undetectable in adults. There is no clinical use for maternal blood or urine estetrol measurements during pregnancy. The clinical use of maternal blood and urine estetrol measurements is of no advantage over the usual estriol assessment."

10. The unexpected pharmacological activity of estetrol is associated with Applicants' discovery that estetrol has a surprisingly long *in vivo* elimination half-life. Applicants' finding that estetrol has a terminal elimination half-life of about 28 hours, which is very much longer than that of the other pregnancy hormone estriol (5-10 minutes), was very unexpected and provided the clue towards its pharmacological usefulness as will be further explained below.

11. It is my understanding that the claims of the pending patent applications that are the subject of this Declaration were rejected as obvious because it has been asserted by USPTO examiners that it is known from the references cited in § 6:

(i) to use estrogens with or without progestins in HRT (reference E1);
(ii) to use a combination of estrogen and progestin in hormonal contraceptives (reference E2);
(iii) to use estrogen to treat decreased libido in women taking GnRH agonists (reference D2); and to use a combination of estrogen and androgen to treat decreased libido in oophorectomized women (reference D3);
(iv) to treat vaginal dryness by administering estrogen (references D1, D4, E3, E4).

12. Assuming that the references cited by the USPTO examiners disclose the information contained in § 11 (i) to (iv), I do not think that, in view of these references, it would have been obvious to use estetrol in pharmacological applications described in § 4. I appreciate that the cited references D1 to D4 contain references to estetrol within a lengthy list of other estrogens. Furthermore, I have read the cited papers published by Holinka et al ("Holinka articles")[1,2], which report that parenterally administered estetrol produced estrogenic changes in the immature rat uterus.

13. I declare that although the cited references D1 to D4 list estetrol among candidate estrogens for pharmaceutical use, it is my view that a person of ordinary skill in the art having knowledge of the aforementioned patent publications D1 to D4 and the "Holinka articles", would not have expected estetrol to be pharmacologically useable for the reasons presented below.

14. The mere mentioning of estetrol in a long list of candidate estrogens in D1 to D4 without any experimental data to support the viability of pharmaceutical uses described in these patents, in my view would not have provided a person of ordinary skill in the art with any motivation to actually employ estetrol in these pharmaceutical uses. Furthermore, the aforementioned US patent publications would not have provided a person of ordinary skill in the art with any motivation to replace the estrogens employed in the uses (i) to (iv) mentioned in §11 with estetrol.

15. In Holinka (1979)[1] the estrogenic activity of estetrol was evaluated by examination of uterine responses to subcutaneous administration of estetrol in doses of 10 and 50 μg/100g body mass. The effects were compared to those obtained by administration of 1 μg/100g body mass estradiol or estriol. The last paragraph of the abstract of Holinka (1979) reads as follows "It is concluded that estetrol administered as a single dose or in 2 doses at a 24 h interval is a weak estrogen which produces effects of short duration. It cannot, however, be considered entirely devoid of estrogenic activity, even though true uterine hyperplasia, as estimated by DNA content, was not promoted by administration of the two 50 μg/100 g bw doses of estetrol".

16. Holinka (1980)[2] describes the results of a study that aimed to extend the study described in Holinka (1979). In this follow-up study estrogenic effects on immature rat uterus of estetrol and the antiestrogen tamoxifen were compared with those of estradiol and estriol. This time, estetrol was injected subcutaneously for 3 days at a dose of 50 μg/100g body mass, a dose 50 times greater than the dosages of estradiol and estriol that were administered subcutaneously (at a dose of 1 μg/100g body mass). The last paragraph of the abstract of Holinka (1980) reads as follows: "In general estradiol treatment promoted the most marked changes, followed by tamoxifen, estriol and estetrol. On the basis of the present biochemical and morphological results, it is concluded that estetrol and tamoxifen have estrogenic effects on the immature rat uterus. However, the estrogenic potency of estetrol, relative to estradiol or estriol was low at the dosage and timing of administration used in these experiments; effects of estetrol introduced in the circulation at a constant rate were not evaluated. These results suggest that the conversion of estradiol to estetrol in the human fetus represent an efficient mechanism of inactivation of the placental hormone." Specifically, even though Holinka et al administered 50 times more estetrol than estradiol or estriol, the observed uterotropic effects of estetrol were still smaller than those of estradiol or estriol. Thus, from Holinka (1980), one of ordinary skill in the art would expect estetrol to be more than 50 times less effective than a weak estrogen, such as estriol.

17. It is my view that a person of ordinary skill in the art would have deduced from the Holinka articles that estetrol has estrogenic activity, but that it is a much weaker estrogen than the already weak estrogen estriol, given that estetrol injected subcutaneous at 50 μg/100g body mass exhibited less estrogenic activity than estriol injected subcutaneous at 1 μg/100g body mass. Estriol is a very weak estrogen due to its low receptor affinity in combination with its very short half-life of 5-10 minutes. Since the Holinka articles teach that estrogenic activity of estetrol is at least 50 times lower than that of a weak estrogen for which very few practical applications exits, the Holinka articles would not have provided a motivation for a person of ordinary skill in the art to investigate the potential pharmacological usefulness of estetrol.

18. Applicants have demonstrated that, contrary to what a person of ordinary skill in the art would have expected, estetrol is pharmacologically very active. The unexpected pharmacological activity of estetrol is associated with its surprisingly long *in vivo* elimination half-life. Whereas, under comparable conditions, the human estrogens estradiol and estriol have terminal elimination half-lifes of about 30 minutes and 5-10 minutes respectively, estetrol has a terminal elimination half-life of about 28 hours. A person of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only 1 hydroxy group and from estradiol by 2 hydroxy groups and (ii) both estriol and estetrol are produced during pregnancy. Hence, Applicants' finding that estetrol has a terminal elimination half-life that is 168-336 higher than that of the other pregnancy hormone

estriol, was very unexpected and provided the clue towards its pharmacological usefulness. Based on my knowledge of the relevant art, I conclude that Applicants are the first to have discovered estetrol's pharmacological usefulness. As explained herein before, it is my view that, prior to June 11, 2002, a person of ordinary skill in the art would not have anticipated this usefulness.

19. In addition, I conclude that Applicants are the first to have discovered estetrol's high oral bioavailability. This finding is truly surprising as other human estrogens, notably estradiol, estriol and estrone, exhibit low oral bioavailability because they are largely metabolized into inactive metabolites during the so called "first pass" through the liver after oral administration. It is my opinion that, given that estetrol's estrogen receptor affinity was known to be considerably lower than that of estradiol and estriol, a person of ordinary skill in the art, being aware that known human estrogens are largely metabolized during the first pass, could not have anticipated the high oral bioavailability of estetrol. Thus, in my view, prior to June 11, 2002, a person of ordinary skill in the art could not have anticipated estetrol's oral pharmacological activity.

20. As mentioned herein before, it is my view that a person of ordinary skill in the art could not have anticipated the advantageous pharmacological properties of estetrol that Applicants have described in the above referenced pending patent applications and that have been reported in scientific articles that were published after June 11, 2002. In particular, such a skilled person could not have foreseen the favorable pharmacokinetic (ADME) and pharmacodynamic properties of estetrol. These favorable properties of estetrol are remarkable since they are much less manifest in other human estrogens, notably estradiol, estriol and estrone. The unexpected favorable properties of estetrol that have been described by Applicants in the aforementioned pending patent applications and that were not known before June 11, 2003 include:

A. Long *in vivo* elimination half-life in the human
   - In the first human study with estetrol, a dose-independent terminal elimination half-life of about 28 hours after single oral administration to early postmenopausal women was demonstrated [4,5]. Terminal elimination half-lifes of the human estrogens estradiol and estriol under comparable conditions are about 30 minutes and 5-10 minutes respectively [3].

B. No binding affinity for sex hormone binding globulin (SHBG)
   - Competitive ligand binding assays did not detect any binding of estetrol to the SHBG steroid-binding sites [4,6]. By contrast, estradiol is bound by SHBG with high affinity [6].

C. No ERα-mediated increase in SHBG production by HepG2 or Hep89 cells
   - Fluorometric assays in wild-type human HepG2 and Hep89 cells showed that estetrol does not stimulate ERα-mediated increases in SHBG production by these cells, in contrast to estradiol and estriol [4,6].

D. No conversion to other active metabolites
   - Estetrol is an end-stage product of estrogen metabolism [4,5,7]. In contrast, especially after oral administration, estradiol is rapidly and reversibly converted by the liver to the estrogenic metabolites estrone and estrone sulfate.

E. No significant inhibition of P450 enzymes
   - At a concentration of 10 μmol/l estetrol has no inhibitory effect on any recombinant human P450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. In contrast, at the same concentration estradiol moderately inhibits CYP1A2 and strongly inhibited CYP2C19 [4,7].

F. Highly selective binding to estrogen receptors ERα and ERβ
   - Estetrol tested at a prime concentration of 10 μmol/l, did not show significant (>20%) inhibition of the binding of the respective ligands in 123 of the 124 assays studied (Estetrol only inhibited binding of prazosin at the adrenergic α_{1B} receptor by 23%) [4,7].

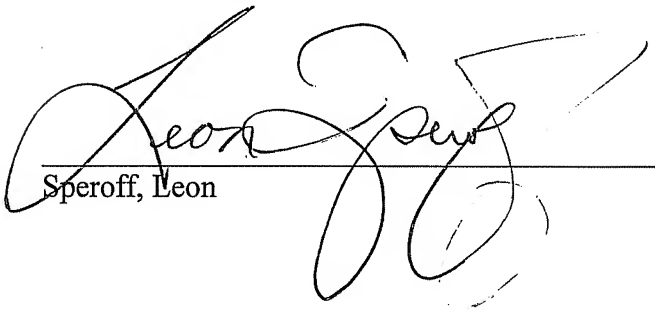
G. Estrogen agonist in bone, vagina, myometrium, endometrium and brain, but estrogen antagonist in breast tumor tissue in the presence of estradiol
   - Estetrol significantly and dose-dependently inhibited the OVX-related increase in osteocalcin levels, increased bone mineral density and content, and increased bone strength [4,8].
   - Estetrol is effective in preventing temperature rises dose-dependently in an animal model considered representative for menopausal vasomotor symptoms [4,9].
   - In the modified Allen-Doisy test estetrol was found to have dose-dependent estrogenic effects on the vagina and on the uterus of ovariectomized rats including the endometrium [4,10].
   - Estetrol at a twice-daily dose of 0.3 mg/kg and above effectively inhibited ovulation in regularly cycling female rats [4,11].
   - Estetrol dose-dependently prevents the growth of chemically induced (DMBA) mammary tumors in rats and has the potential to reduce the number and size of pre-existing mammary tumors [4,12]. By contrast it is well-established that estradiol has proliferative effects on breast tumor cells and tissue.

H. Oral absorption in the human with a strong dose-response relationship suggesting high oral bioavailability
   - In a first-in-human study four single doses of 0.1, 1, 10 and 100 mg estetrol were administered orally to early postmenopausal women. High oral bioavailability, a strong dose-response relationship and a long elimination half-life (see A) were found. For the first time (oral) pharmacodynamic effects of estetrol were observed since the data showed a strong suppression of follicle stimulating hormone (FSH) with the 100 mg dose and a dose-dependent inhibition of luteinizing hormone (LH) levels [4,5].

The above mentioned features A to D imply that the estrogenic activity of estetrol is much more pronounced than could have been anticipated on the basis of the estrogen receptor affinity studies described in scientific literature before June 11, 2002. Features E and F indicate that it is unlikely that estetrol administration will induce undesirable side-effects. Feature G indicates that estetrol may suitably be used as a drug in estrogen or hormone replacement therapy (ERT/HRT) including the prevention of osteoporosis (US 10/478,262), the treatment of female sexual dysfunction (US 10/478,264), topical treatment of vaginal atrophy (US 10/517,509) and as the estrogenic component in contraceptives (US 10/478,357). Feature H indicates that estetrol has potential as a once-a-day oral drug for human use.

21. I have not been compensated for the execution of this declaration, or any time I spent relating to this declaration.

22. I declare further that all statements made herein are true to my knowledge; and that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Speroff, Leon

8-26-08

Date

References

[1] Holinka et al., *In vivo effects of estetrol on the immature rat uterus.* Biol Reprod 20 (1979) 242-6.

[2] Holinka et al., *Comparison of effects of estetrol and tamoxifen with those of estriol and estradiol on the immature rat uterus.* Biol Reprod 22 (1980) 913-26.

[3] Leon Speroff, Robert H. Glass and Nathan G. Kase. *Clinical Gynecologic Endocrinology and Infertility.* Baltimore, Maryland, USA. Lippincott Williams & Wilkins, 1999.

[4] Coelingh Bennink et al., *Estetrol Review: profile and potential clinical applications*, Climacteric 2008; 11 (Suppl 1): 47-58

[5] Visser et al., *First human exposure to exogenous single-dose oral estetrol in early postmenopausal women*, Climacteric 2008; 11 (Suppl 1): 31-40

[6] Hammond et al., *Estetrol does not bind sex hormone binding globulin or increase its production by human HepG2 cells*, Climacteric 2008; 11 (Suppl 1): 41-46

[7] Visser et al., *In vitro effects of estetrol on receptor binding, drug targets and human liver cell metabolism*, Climacteric 2008; 11 (Suppl 1): 64-68

[8] Coelingh Bennink et al., *Oral bioavailability and bone-sparing effects of estetrol in an osteoporosis model*, Climacteric 2008; 11 (Suppl 1): 2-14

[9] Holinka et al., *Preventive effect of oral estetrol in a menopausal hot flush model*, Climacteric 2008; 11 (Suppl 1): 15-21

[10] Heegaard et al., *Estrogenic uterovaginal effects of oral estetrol in the modified Allen-Doisy test*, Climacteric 2008; 11 (Suppl 1): 22-28

[11] Coelingh Bennink et al., *Ovulation inhibition by estetrol in an in vivo model*, Contraception 2008; 77: 186-190

[12] Coelingh Bennink et al., *Estetrol, a pregnancy specific human steroid, prevents and suppresses mammary tumor growth in a rat model*, Climacteric 2008; 11 (Suppl 1): 29

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/478,365 Confirmation No. 3870
Applicants	:	Evert J. BUNSCHOTEN et al.
Filed	:	May 25, 2004
Title	:	DRUG DELIVERY SYSTEM COMPRISING A TETRAHYDROXYLATED ESTROGEN FOR USE IN HORMONAL CONTRACEPTION
Group Art Unit	:	1616
Examiner	:	Mei Ping CHUI
Customer No.	:	28289
Application No.	:	10/517,686 Confirmation No. 3094
Applicants	:	Evert J. BUNSCHOTEN et al.
Filed	:	June 30, 2005
Title	:	METHOD OF TREATING OR PREVENTING IMMUNE MEDIATED DISORDERS AND PHARMACEUTICAL FORMULATION FOR USE THEREIN
Group Art Unit	:	1616
Examiner	:	Mei Ping CHUI
Customer No.	:	28289
Application No.	:	10/521,040 Confirmation No. 6630
Applicants	:	Herman J. T. Coelingh Bennink et al.
Filed	:	August 16, 2005
Title	:	PHARMACEUTICAL COMPOSITION COMPRISING ESTETROL DERIVATIVES FOR USE IN CANCER THERAPY
Group Art Unit	:	1616
Examiner	:	Mei Ping CHUI
Customer No.	:	28289

DECLARATION

I, Speroff, Leon declare and state the following:

1. A detailed listing of my publications, together with details of my education, are given in my *curriculum vitae* which is attached as Exhibit A.

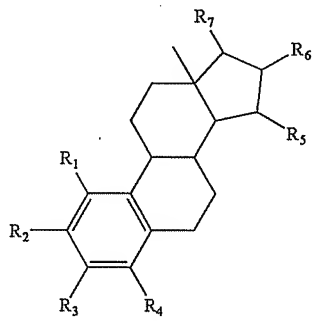
2. Based on my academic training and professional experience, I consider myself an expert in the field of estrogen-related therapies and treatments, and I was such a person in 2001 and 2002.

3. I have received copies of patent applications that I understand were filed in the United States and correspond to the above-captioned applications.

4. I understand that the above mentioned patent applications relate to:

- new methods of contraception (Appln. No. 10/478,365);
- new methods of treating cancer (Appln. No. 10/521,040);
- a new method of treating immune mediated disorders (Appln. No. 10/517,686);

The aforementioned methods have in common that they comprise administration of the following estrogenic component:



wherein R_1, R_2, R_3 and R_4 independently are a hydrogen atom, a hydroxyl group or an alkoxy group with 1-5 carbon atoms. R_5, R_6 and R_7 are hydroxyl groups. No more than three of R_1, R_2, R_3 and R_4 are hydrogen atoms. The invention also includes using variations of this formula, such as precursors capable of liberating a substance according to the aforementioned formula and mixtures of one or more of the aforementioned substances and/or precursors. One embodiment of the aforementioned formula is estetrol.

5. I have also received copies of Office Actions that have been issued in relation to the above referenced pending patent applications, with the exception of Appln. No. 10/532,320 for which I have been told no Office Action has been issued as of yet. Specifically, I have received copies of the following Office Actions:

OA-1 - 10/478,365 (Final Office Action mailed on April 1, 2008)
OA-2 - 10/517,686 (Final Office Action mailed on April 4, 2008)
OA-3 - 10/521,040 (Final Office Action mailed on April 2, 2008).

6. I have further received copies of the following references that I have been told have been cited in the above mentioned Office Actions against the independent claims of the above referenced pending patent applications.

Publications mentioning estetrol:

D1 US 5,211,952 (Spicer et al.) – cited in OA-1

D2 US 5,340,584 (Spicer et al.) – cited in OA-2 and OA-3

D3 Holinka, Biology of Reproduction, 1980; 20(4): 913-926 [2] – cited in OA-3

Publications not mentioning estetrol:

E1 US 6,214,815 (Shangold et al.) – cited in OA-1

E2 US 2002/0156059 (Elliesen) – cited in OA-3

E3 US 2002/0183299 (Voskuhl) – cited in OA-2

It is my understanding that the independent claims of the pending patent applications that are the subject of this Declaration were rejected as being unpatentable over the above cited references under 35 U.S.C. 103(a) (obviousness). I have been asked to comment on my understanding of the state of the art prior to June 11, 2002, which I understand is the priority date for Appln. No. 10/517,686. Particularly, I have been asked whether, prior to June 11, 2002, a person of ordinary skill in the art would have considered it obvious to use estetrol in the pharmacological application listed in § 4. More particularly, I have been asked whether, prior to the June 11, 2002, a person of ordinary skill in the art would have been motivated to use estetrol in the pharmacological applications listed in § 4, and whether the discovery that estetrol was pharmacologically useful in these applications is unexpected and surprising.

7. It is my view that, prior to June 11, 2002, for the reasons presented below, a person of ordinary skill in the art would not have expected estetrol to be pharmacologically useable, and that the Applicants were the first to discover the pharmacological usefulness of estetrol. In addition, and more particularly, it is my opinion that, prior to June 11, 2002, a person of ordinary skill in the art:

- would not have expected estetrol to be pharmacologically active when orally administered.
- would not have expected that estetrol can be used to treat estrogen-sensitive breast cancer.

8. I declare that before June 11, 2002 I had no knowledge of any concrete pharmacological application of estetrol. Furthermore, before June 11, 2002, I did not expect that estetrol can be used effectively as a drug in therapeutic treatments or in hormonal contraceptives. Based on the data from scientific literature that was available before June 11, 2002, I would have expected estrogenic activity of estetrol to be too low for pharmacological applications, such as the ones recited in Applicants' claims.

9. My view that a person of ordinary skill in the art would not have expected estetrol to be pharmacologically active is supported by leading textbooks in the field of endocrinology. In "Clinical Gynecologic Endocrinology and Infertility" [3] estetrol is solely mentioned in Chapter 8 (The Endocrinology of Pregnancy) under the subheading "Measurement of Estrogen in Pregnancy" (page 287) and in the index. On page 287 it is stated that "Estetrol (15alpha-hydroxyestriol) is formed from a fetal precursor and is very dependent on 15alpha-hydroxylation activity in the fetal liver. The capacity for 15alpha-hydroxylation of estrogens increases during fetal life, reaching maximum at term. This activity then declines during infancy and is low, absent or undetectable in adults. There is no clinical use for maternal blood or urine estetrol measurements during pregnancy. The clinical use of maternal blood and urine estetrol measurements is of no advantage over the usual estriol assessment."

10. The unexpected pharmacological activity of estetrol is associated with Applicants' discovery that estetrol has a surprisingly long *in vivo* elimination half-life. Applicants' finding that estetrol has a terminal elimination half-life of about 28 hours, which is very much longer than that of the other pregnancy hormone estriol (5-10 minutes), was very

unexpected and provided the clue towards its pharmacological usefulness as will be further explained below.

11. It is my understanding that the claims of the pending patent applications that are the subject of this Declaration were rejected as obvious because it has been asserted by USPTO examiners that it is known from the references cited in § 6:

(i) to use a combination of estrogen and progestin in hormonal contraceptives (reference D1, E1);

(ii) to use a combination of estrogen and aromatase inhibitor for selective estrogen replacement therapy to reduce the risk of breast cancer (reference E2);

(iii) to use orally administered estrogen (estriol) in the treatment of auto-immune diseases (reference E3).

12. Assuming that the references cited by the USPTO examiners disclose the information contained in § 11 (i) to (vi), I do not think that, in view of these references, it would have been obvious to use estetrol in pharmacological applications described in § 4. I appreciate that the cited references D1 to D4 contain references to estetrol within a lengthy list of other estrogens. Furthermore, I have read the cited paper published by Holinka et al ("Holinka articles")[1], which reports that parenterally administered estetrol produced estrogenic changes in the immature rat uterus.

13. I declare that although the cited references D1 and D2 list estetrol among candidate estrogens for pharmaceutical use, it is my view that a person of ordinary skill in the art having knowledge of the aforementioned patent publications D1 and D2 and the "Holinka article", would not have expected estetrol to be pharmacologically useable for the reasons presented below.

14. The mere mentioning of estetrol in a long list of candidate estrogens in D1 and D2 without any experimental data to support the viability of pharmaceutical uses described in these patents, in my view would not have provided a person of ordinary skill in the art with any motivation to actually employ estetrol in these pharmaceutical uses. Furthermore, the aforementioned US patent publications would not have provided a person of ordinary skill in the art with any motivation to replace the estrogens employed in the uses (i) to (iii) mentioned in §11 with estetrol.

15. Holinka (1980)[1] describes the results of a study in which estrogenic effects on immature rat uterus of estetrol and the antiestrogen tamoxifen were compared with those of estradiol and estriol. Estetrol was injected subcutaneously for 3 days at a dose of 50 µg/100g body mass, a dose 50 times greater than the dosages of estradiol and estriol that were administered subcutaneously (at a dose of 1 µg/100g body mass). The last paragraph of the abstract of Holinka (1980) reads as follows: "In general estradiol treatment promoted the most marked changes, followed by tamoxifen, estriol and estetrol. On the basis of the present biochemical and morphological results, it is concluded that estetrol and tamoxifen have estrogenic effects on the immature rat uterus. However, the estrogenic potency of estetrol, relative to estradiol or estriol was low at the dosage and timing of administration used in these experiments; effects of estetrol introduced in the circulation at a constant rate were not evaluated. These results suggest that the conversion of estradiol to estetrol in the human fetus represent an efficient mechanism of inactivation of the placental hormone." Specifically, even though

Holinka et al administered 50 times more estetrol than estradiol or estriol, the observed uterotropic effects of estetrol were still smaller than those of estradiol or estriol. Thus, from Holinka (1980), one of ordinary skill in the art would expect estetrol to be more than 50 times less effective than a weak estrogen, such as estriol.

16. It is my view that a person of ordinary skill in the art would have deduced from the Holinka article that estetrol has estrogenic activity, but that it is a much weaker estrogen than the already weak estrogen estriol, given that estetrol injected subcutaneous at 50 μg/100g body mass exhibited less estrogenic activity than estriol injected subcutaneous at 1 μg/100g body mass. Estriol is a very weak estrogen due to its low receptor affinity in combination with its very short half-life of 5-10 minutes. Since the Holinka article teaches that estrogenic activity of estetrol is at least 50 times lower than that of a weak estrogen for which very few practical applications exits, the Holinka article would not have provided a motivation for a person of ordinary skill in the art to investigate the potential pharmacological usefulness of estetrol.

17. Applicants have demonstrated that, contrary to what a person of ordinary skill in the art would have expected, estetrol is pharmacologically very active. The unexpected pharmacological activity of estetrol is associated with its surprisingly long *in vivo* elimination half-life. Whereas, under comparable conditions, the human estrogens estradiol and estriol have terminal elimination half-lifes of about 30 minutes and 5-10 minutes respectively, estetrol has a terminal elimination half-life of about 28 hours. A person of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only 1 hydroxy group and from estradiol by 2 hydroxy groups and (ii) both estriol and estetrol are produced during pregnancy. Hence, Applicants' finding that estetrol has a terminal elimination half-life that is 168-336 higher than that of the other pregnancy hormone estriol, was very unexpected and provided the clue towards its pharmacological usefulness. Based on my knowledge of the relevant art, I conclude that Applicants are the first to have discovered estetrol's pharmacological usefulness. As explained herein before, it is my view that, prior to June 11, 2002, a person of ordinary skill in the art would not have anticipated this usefulness.

18. In addition, I conclude that Applicants are the first to have discovered estetrol's high oral bioavailability. This finding is truly surprising as other human estrogens, notably estradiol, estriol and estrone, exhibit low oral bioavailability because they are largely metabolized into inactive metabolites during the so called "first pass" through the liver after oral administration. It is my opinion that, given that estetrol's estrogen receptor affinity was known to be considerably lower than that of estradiol and estriol, a person of ordinary skill in the art, being aware that known human estrogens are largely metabolized during the first pass, could not have anticipated the high oral bioavailability of estetrol. Thus, in my view, prior to June 11, 2002, a person of ordinary skill in the art could not have anticipated estetrol's oral pharmacological activity.

19. Finally, I conclude that Applicants are the first to have discovered the use of estetrol in the treatment of estrogen-sensitive breast cancer. It is widely accepted that estrogens have a stimulatory proliferative effect on estrogen sensitive breast cancer. This is why female patients having such breast cancer are frequently treated with, for example, anti-estrogens and/or aromatase inhibitors in order to suppress the synthesis/effect of endogenous estrogens, notably

estradiol. In contrast to the human estrogens, especially estradiol, and also in contrast to all synthetic estrogens, estetrol counteracts the estrogenic activity that stimulates proliferation of estrogen-sensitive breast cancer. Due to this selective estrogen activity, some pharmacologists would regard estetrol as a Selective Estrogen Receptor Modulator (SERM) rather than an estrogen. In my opinion, prior to June 11, 2002, a person of ordinary skill in the art could not have foreseen the selective estrogen antagonistic activity of estetrol and consequently, before that date a skilled person would not have contemplated using estetrol in the treatment of estrogen sensitive breast cancer.

20. As mentioned herein before, it is my view that a person of ordinary skill in the art could not have anticipated the advantageous pharmacological properties of estetrol that Applicants have described in the above referenced pending patent applications and that have been reported in scientific articles that were published after June 11, 2002. In particular, such a skilled person could not have foreseen the favorable pharmacokinetic (ADME) and pharmacodynamic properties of estetrol. These favorable properties of estetrol are remarkable since they are much less manifest in other human estrogens, notably estradiol, estriol and estrone. The unexpected favorable properties of estetrol that have been described by Applicants in the aforementioned pending patent applications and that were not known before June 11, 2003 include:

A. Long *in vivo* elimination half-life in the human
   - In the first human study with estetrol, a dose-independent terminal elimination half-life of about 28 hours after single oral administration to early postmenopausal women was demonstrated [4,5]. Terminal elimination half-lifes of the human estrogens estradiol and estriol under comparable conditions are about 30 minutes and 5-10 minutes respectively [2].

B. No binding affinity for sex hormone binding globulin (SHBG)
   - Competitive ligand binding assays did not detect any binding of estetrol to the SHBG steroid-binding sites [3,5]. By contrast, estradiol is bound by SHBG with high affinity [5].

C. No ERα-mediated increase in SHBG production by HepG2 or Hep89 cells
   - Fluorometric assays in wild-type human HepG2 and Hep89 cells showed that estetrol does not stimulate ERα-mediated increases in SHBG production by these cells, in contrast to estradiol and estriol [3,5].

D. No conversion to other active metabolites
   - Estetrol is an end-stage product of estrogen metabolism [3,4,6]. In contrast, especially after oral administration, estradiol is rapidly and reversibly converted by the liver to the estrogenic metabolites estrone and estrone sulfate.

E. No significant inhibition of P450 enzymes
   - At a concentration of 10 µmol/l estetrol has no inhibitory effect on any recombinant human P450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. In contrast, at the same concentration estradiol moderately inhibits CYP1A2 and strongly inhibited CYP2C19 [3,6].

F. Highly selective binding to estrogen receptors ERα and ERβ

- Estetrol tested at a prime concentration of 10 μmol/l, did not show significant (>20%) inhibition of the binding of the respective ligands in 123 of the 124 assays studied (Estetrol only inhibited binding of prazosin at the adrenergic α_{1B} receptor by 23%) [3,6].

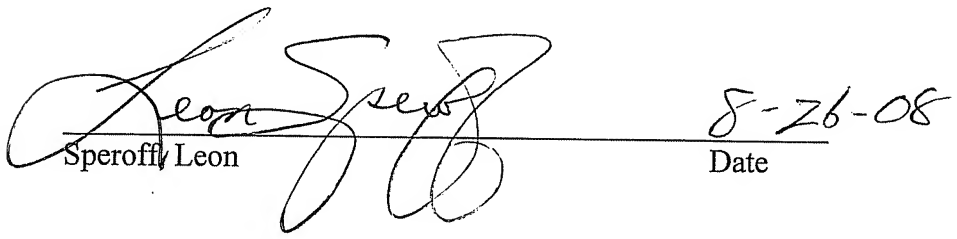
G. Estrogen agonist in bone, vagina, myometrium, endometrium and brain, but estrogen antagonist in breast tumor tissue in the presence of estradiol
   - Estetrol significantly and dose-dependently inhibited the OVX-related increase in osteocalcin levels, increased bone mineral density and content, and increased bone strength [3,7].
   - Estetrol is effective in preventing temperature rises dose-dependently in an animal model considered representative for menopausal vasomotor symptoms [3,8].
   - In the modified Allen-Doisy test estetrol was found to have dose-dependent estrogenic effects on the vagina and on the uterus of ovariectomized rats including the endometrium [3,9].
   - Estetrol at a twice-daily dose of 0.3 mg/kg and above effectively inhibited ovulation in regularly cycling female rats [3,10].
   - Estetrol dose-dependently prevents the growth of chemically induced (DMBA) mammary tumors in rats and has the potential to reduce the number and size of pre-existing mammary tumors [3,11]. By contrast it is well-established that estradiol has proliferative effects on breast tumor cells and tissue.

H. Oral absorption in the human with a strong dose-response relationship suggesting high oral bioavailability
   - In a first-in-human study four single doses of 0.1, 1, 10 and 100 mg estetrol were administered orally to early postmenopausal women. High oral bioavailability, a strong dose-response relationship and a long elimination half-life (see A) were found. For the first time (oral) pharmacodynamic effects of estetrol were observed since the data showed a strong suppression of follicle stimulating hormone (FSH) with the 100 mg dose and a dose-dependent inhibition of luteinizing hormone (LH) levels [3,4].

The above mentioned features A to D imply that the estrogenic activity of estetrol is much more pronounced than could have been anticipated on the basis of the estrogen receptor affinity studies described in scientific literature before June 11, 2002. Features E and F indicate that it is unlikely that estetrol administration will induce undesirable side-effects. Feature G indicates that estetrol may suitably be used as a drug for the treatment of estrogen dependent breast cancer (US 10/521,040), the treatment of auto-immune diseases (US 10/517,686) and as the estrogenic component in contraceptives (US 10/478,365). Feature H indicates that estetrol has potential as a once-a-day oral drug for human use.

21. I have not been compensated for the execution of this declaration, or any time I spent relating to this declaration.

22. I declare further that all statements made herein are true to my knowledge; and that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Speroff, Leon — Date: 8-26-08

References

1 Holinka et al., *Comparison of effects of estetrol and tamoxifen with those of estriol and estradiol on the immature rat uterus.* Biol Reprod 22 (1980) 913-26.

2 Leon Speroff, Robert H. Glass and Nathan G. Kase. *Clinical Gynecologic Endocrinology and Infertility.* Baltimore, Maryland, USA. Lippincott Williams & Wilkins, 1999.

3 Coelingh Bennink et al., *Estetrol Review: profile and potential clinical applications*, Climacteric 2008; 11 (Suppl 1): 47-58

4 Visser et al., *First human exposure to exogenous single-dose oral estetrol in early postmenopausal women*, Climacteric 2008; 11 (Suppl 1): 31-40

5 Hammond et al., *Estetrol does not bind sex hormone binding globulin or increase its production by human HepG2 cells*, Climacteric 2008; 11 (Suppl 1): 41-46

6 Visser et al., *In vitro effects of estetrol on receptor binding, drug targets and human liver cell metabolism*, Climacteric 2008; 11 (Suppl 1): 64-68

7 Coelingh Bennink et al., *Oral bioavailability and bone-sparing effects of estetrol in an osteoporosis model*, Climacteric 2008; 11 (Suppl 1): 2-14

8 Holinka et al., *Preventive effect of oral estetrol in a menopausal hot flush model*, Climacteric 2008; 11 (Suppl 1): 15-21

9 Heegaard et al., *Estrogenic uterovaginal effects of oral estetrol in the modified Allen-Doisy test*, Climacteric 2008; 11 (Suppl 1): 22-28

10 Coelingh Bennink et al., *Ovulation inhibition by estetrol in an in vivo model*, Contraception 2008; 77: 186-190

11 Coelingh Bennink et al., *Estetrol, a pregnancy specific human steroid, prevents and suppresses mammary tumor growth in a rat model*, Climacteric 2008; 11 (Suppl 1): 29

EXHIBIT "A"

LEON SPEROFF

CURRICULUM VITAE

BIRTHDATE: July 2, 1935 **BIRTHPLACE:** Lorain, Ohio

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Oregon Health & Science University
3181 SW Sam Jackson Park Road
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EDUCATION

B.A. Denison University, Granville, Ohio June, 1957

M.D. Case Western Reserve University School of Medicine
Cleveland, Ohio June, 1961

PROFESSIONAL TRAINING

Rotating Intern, University Hospitals of Cleveland, Ohio: July, 1961 - June, 1962.

Assistant Resident in Obstetrics and Gynecology, Yale-New Haven Hospital, New Haven, Connecticut: July, 1962 - June, 1965.

Chief Resident in Obstetrics and Gynecology, Yale-New Haven Hospital, New Haven, Connecticut: July, 1965 - June, 1966.

MILITARY SERVICE

Obstetrician-Gynecologist, USAF Hospital, Vandenberg Air Force Base, California, July, 1966 - June, 1968.

FELLOWSHIP TRAINING

Fellow in the Training Program for Steroid Biochemistry at the Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, October, 1968 - September, 1969.

Research Associate, Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, New York, New York, September, 1969 - June, 1970.

SPECIALTY CERTIFICATION

Diplomate of the American Board of Obstetrics and Gynecology, November, 1968.

Subspecialty Certification in the Division of Reproductive Endocrinology, American Board of Obstetrics and Gynecology, November, 1974.

ACADEMIC APPOINTMENTS

Assistant Professor of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut, July, 1970 - June, 1974.

Director of Gynecologic Endocrine Laboratory, Yale University School of Medicine, New Haven, Connecticut, July, 1970 - November, 1976.

Associate Professor of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut, July, 1974 - November, 1976.

Assistant Chairman of the Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut, November, 1975 - November, 1976.

Professor and Chairman of the Department of Obstetrics and Gynecology, School of Medicine, Oregon Health Sciences University, Portland, Oregon, November, 1976 - July, 1983.

Arthur H. Bill Professor and Chairman of the Department of Reproductive Biology, Case Western Reserve University School of Medicine, Cleveland, Ohio, August, 1983 - January, 1988.

William H. Weir Professor of Reproductive Biology, Case Western Reserve University School of Medicine, Cleveland, Ohio, January, 1988 - June, 1989.

Professor of Obstetrics and Gynecology, School of Medicine, Oregon Health & Science University, Portland, Oregon, June, 1989 – 2006,

Professor Emeritus of Obstetrics and Gynecology, School of Medicine, Oregon Health & Science Univrsity, Portland, Oregon, 2006 -

HOSPITAL APPOINTMENTS

Director, Department of Obstetrics and Gynecology, University Hospitals of Cleveland, Ohio, August, 1983 - January, 1988.

General Manager, The MacDonald Hospital for Women, University Hospitals of Cleveland, Ohio, September 1984 - April, 1987.

Director, The Women's Health Research Unit, University Hospitals, Oregon Health Sciences University, 1989 - 2003

NATIONAL ORGANIZATIONS

The Endocrine Society
Society for the Study of Reproduction
American College of Obstetricians and Gynecologists
American Fertility Society
Society for Gynecologic Investigation
American Association for the Advancement of Science
Sigma Xi
Association of Professors of Gynecology and Obstetrics
American Gynecological and Obstetrical Society
Society of Reproductive Endocrinologists
Central Association of Obstetricians and Gynecologists
European Society of Human Reproduction and Embryology
Planned Parenthood Federation of America
Association of Reproductive Health Professionals
Jacobs Institute of Women's Health (Founding Member)
North American Menopause Society

REGIONAL ORGANIZATIONS

New Haven Obstetrical Society, 1971 – 1976.
Oregon Medical Association, 1976 –1983; 1989 –.
Multnomah County Medical Society (Oregon), 1976 –1983; 1989 –.
Oregon Society of Obstetricians and Gynecologists, 1976 – 1983.
Portland Society of Obstetricians and Gynecologists, 1976 - 1983, 1989 –.
Pacific Northwest Obstetrical and Gynecological Association, 1976 –.
Pacific Coast Fertility Society, 1976 –.
Pacific Coast Obstetrical and Gynecological Society, 1981 –.
Cleveland Society of Obstetricians and Gynecologists, 1983 - 1989.
Ohio State Medical Association, 1983 - 1989.
Cleveland Academy of Medicine, 1983 - 1989.

NATIONAL ACTIVITIES

American College of Obstetricians and Gynecologists

Gynecologic Endocrinology and Infertility Task Force of the Learning Resources Commission, 1977 - 1978.
Editorial Board, PRECIS, 1979 - 1987.
Committee on Gynecologic Practice:
Chairman, Subcommittee on Reproductive Endocrinology, 1982-1986.
Committee Chairman, 1986 - 1989.
Chairman, Task Force on Aging, 1989
Section Editor on Preventive Health Care, PROLOG, 1994.

American Society for Reproductive Medicine (formerly the American Fertility Society)

Chairman, Postgraduate Program for 1982.
Public Affairs Committee, 1981 - 1983.
Board of Directors, 1986 - 1989.
Finance Committee, 1986 - 1989.
Chairman of Finance Committe, 1988-1989.
Program Policy Committe, 1988.

President, 1991-1992.
President's Council, 1989-1994.
Program Policy Committee, 1989-1992.
Nominating Committee, 1989-1994.
Long Range Planning Committee, 1989-1994.

Chairman, Practice Commitee, 1989-1991.

Chairman, The Research Career Development Committee, 1992-1996.

Representative, CAS/AAMC, 1997-2000.

American Board of Obstetrics and Gynecology

Examiner, 1976 - 1979.
Examiner, Division of Reproductive Endocrinology, 1979 - 1983.

Association of Professors of Gynecology and Obstetrics

Committee on Academic Manpower and Recruitment, 1980 - 1983.
Nominating Committee for Officers, 1983.

Basil O'Connor Starter Research Advisory Committee, The National Foundation March of Dimes, 1979 - 1989.

Pacific Coast Fertility Society

Program Chairman, 1979.
Board of Directors, 1980 - 1982.

Society for Gynecologic Investigation

Representative, Liaison Committee for Obstetrics and Gynecology, 1981 - 1983.

Society of Reproductive Endocrinologists

Founding President, 1983 - 1984.

The Berlex Foundation

Board of Trustees, 1985 - 2000

The Planned Parenthood Federation

National Medical Committee, 1987 - 1990
Nominating Committee 1989

North American Menopause Society
Board of Trustees, 2004-
Editorial Board, *Menopause*
Annual Meeting, Scientific Committee, 2004
Secretary, 2006-2008
Executive Committee, 2008
Chair, Memberschip Committee, 2005–2008
Program Committee, 2007-2008
Chair, Program Committee, 2009

LOCAL ACTIVITIES

Oregon Health Sciences University

Space Committee, 1978.
ad hoc Committee of Chairmen on Tenure, 1977.
Faculty Council
Co-Director, Conjoint Pathophysiology Course on Reproduction for Second Year Students, 1977 - 1983, 1990.
ad hoc Long Range Planning Committee, 1980.
Search Committee, Chairman of Anesthesia, 1980 - 1981.
Chairman, Task Force on Human Development, School of Medicine, New Curriculum, 1991.
Chairman, Departmental Promotions and Tenure Committee, 1992- 2002
Chairman, Drug Utilization and Evaluation Committee, 1993-1995

Planned Parenthood Association of Portland, Oregon

Medical Advisory Board, 1976 - 1983; 1989- 2000
Chairman, 1994 -1996.

Portland Area Childbirth Educators Association

Medical Advisory Board, 1976 - 1983.

Northwest Oregon Health Systems

Technical Advisory Panel on Obstetrical Services, 1980 - 1983.

Oregon High School Hockey League

President, 1979 - 1980.

University Hospitals of Cleveland, Ohio

Committee on Residency Training, 1983-1987.
Operating Room Committee, 1983-1987.
Executive Committee, Medical Council, 1983-1987.

Case Western Reserve University School of Medicine

Committee on Continuing Education, 1984 - 1987.
Dean's Executive Committee, 1983-1987.
Committee on Medical Education, 1984 - 1987.

Cleveland Regional Perinatal Network
Chairman, 1984 - 1988

Citzens for the Preservation of Skyline Ridge

Treasurer, 1989 - 1999

Northwest Horse Council

Father of the Year, 1999

PUBLICATIONS

PAST EDITORIAL ACTIVITIES

Co-Founder and Co-Editor, 1972 - 1975, Associate Editor, 1975 - 1977, PROSTAGLANDINS, a bimonthly journal, Geron-X, Inc.

Editor-in-chief, ADVANCES IN REPRODUCTIVE MEDICINE, Medical Economics, 1982 - 1984.

Executive Editor, WOMEN'S HEALTH CONSENSUS, Health Learning Systems, Inc., 1989 - 1990.

Editorial Board, POSTGRADUATE OBSTETRICS AND GYNECOLOGY, 1979 - 1995.

Editorial Board, FERTILITY AND STERILITY, American Fertility Society, 1980 - 1984.

Editorial Board, JOURNAL CLUB, OBSTETRICS AND GYNECOLOGY, Omega Communications, 1980 - 1986.

Editorial Board, CLINICAL AND EXPERIMENTAL HYPERTENSION IN PREGNANCY, Marcel Dekker, 1982 - 1983.

Editorial Board, VIDEO JOURNAL OF OBSTETRICS AND GYNECOLOGY, Medical Video Productions, 1987 - 1994.

Consulting Editor, YOUR PATIENT & FITNESS, McGraw Hill, 1987-1988.

Editor-in-chief, MENOPAUSAL MEDICINE, 1992-1995.

Editor-in-chief, WOMEN'S HEALTH REPORTS, 1995 - 1996.

Editorial Board, THE ENDOCRINOLOGIST, 1994 – 1998.

Editor-in-chief, SEMINARS IN REPRODUCTIVE ENDOCRINOLOGY, Thieme-Stratton, 1983-2000.

Editorial Board, PRIMARY CARE UPDATE FOR OB/GYNS, 1994 – 2000.

CURRENT EDITORIAL ACTIVITIES

Editor-in-chief, OB/GYN CLINICAL ALERT, American Health Consultants, 1984 -

Editorial Board, CONTEMPORARY OB/GYN, Medical Economics, 1972 -

Editorial Board, DIALOGUES IN CONTRACEPTION, Health Learning Systems, Inc., 1990 –

Editorial Board, MENOPAUSE, North American Menopause Society, 2004 -

TELEVISION

Medical Host, Obstetrics and Gynecology, Lifetime Cable Television, 1988-1990.

BOOKS - AUTHORED

Speroff L, Glass RH, Kase, NG, CLINICAL GYNECOLOGIC ENDOCRINOLOGY AND INFERTILITY, Williams & Wilkins, Baltimore, 1973; Spanish Edition, 1975, Portuguese Edition, 1976; Serbo-Croatian Edition, 1978.

Second Edition, 1978; Spanish Edition, 1980; Portuguese Edition, 1980;

Third Edition, 1983; Portuguese Edition, 1986; Italian Edition, 1986; Spanish Edition, 1986; Farsi Edition, 1988.

Fourth Edition, 1989; German Edition, 1989; Italian Edition, 1992

Fifth Edition, 1994; Portugese Edition, 1995; Turkish Edition, 1996; Italian Edition, Greek Edition 1997.

Sixth Edition, 1999; Spanish Edition, 2000; Chinese Edition, 2003.

Speroff L, Fritz MA, CLINICAL GYNECOLOGIC ENDOCRINOLOGY AND INFERTILITY, Lippincott Williams & Wilkins, Baltimore, Seventh Edition, 2005.

Turkish Edition, 2005; Brazilian Edition, 2006.

Spanish Edition, 2006.

Polish Edition, 2007.

Gordon JD, Speroff L, HANDBOOK FOR CLINICAL GYNECOLOGIC ENDOCRINOLOGY AND INFERTILITY, Lipppincott Williams & Wilkins, 2002.

Turkish Edition, 2003; Chinese Edition, 2005.

Byyny RL, Speroff, L, A CLINICAL GUIDE FOR THE CARE OF OLDER WOMEN, Williams & Wilkins, Baltimore, 1990; Spanish Edition (Argentina), 1991.

Second Edition, 1996.

Russian Edition, 2001

Speroff L, Darney PD, A CLINICAL GUIDE FOR CONTRACEPTION, Williams & Wilkins, Baltimore, 1992; Portugese edition, 1995.

Second Edition, 1996; Indonesian edition, 1997; Spanish edition, 1999; Japanese edition, 1999.

Third Edition, 2001.

Fourth Edition, 2005.

Polish Edition, 2007.

Siefer DB, Speroff L, CLINICAL GYNECOLOGIC ENDOCRINOLOGY AND INFERTILITY: SELF ASSESSMENT AND STUDY GUIDE, Williams & Wilkins, Baltimore, 1995.

Second Edition, 1999.

Speroff L, MANAGING MENOPAUSE. A CLINICIAN'S GUIDEBOOK, Thomson Medical Economics, Montvale, New Jersey, 2002.

Speroff L, CARLOS MONTEZUMA, M.D. A YAVAPAI AMERICAN HERO. THE LIFE AND TIMES OF AN AMERICAN INDIAN, 1866–1923, Arnica Publishing, Inc., Portland, 2003.

Second Edition, 2005.

Speroff L, A CLINICIAN'S GUIDEBOOK. MENOPAUSE. GUIDELINES FOR CONTEMPORARY MANAGEMENT, Advanstar Communications, Medvale, New Jersey, 2006.

Speroff L, THE DESCHUTES RIVER RAILROAD WAR, Arnica Publishing, Inc., Portland, 2007.

Speroff L, A SLOW-PITCH SUMMER. MY ROOKIE SENIOR SOFTBALL SEASON, Arnica Publishing, Inc., Portland, 2007.

Speroff L, A GOOD MAN. GREGORY GOODWIN PINCUS. THE MAN, HIS STORY, THE BIRTH CONTROL PILL, Arnica Publishing, Inc., Portland, in preparation.

BOOKS - EDITED

Speroff L, Simpson JL, editors, GYNECOLOGY AND OBSTETRICS, VOLUME V, REPRODUCTIVE ENDOCRINOLOGY, INFERTILITY, AND GENETICS, Harper & Row, 1981-1999, annual revisions.

Wenger NK, Speroff L, Packard B, editors, CARDIOVASCULAR HEALTH AND DISEASE IN WOMEN, Lejacq Communications, Inc., Greenwich, Connecticut, 1993.

Lorrain J, Plouffe L Jr, Ravnikar V, Speroff L, Watts N, editors, COMPREHENSIVE MANAGEMENT OF MENOPAUSE, Springer-Verlag, New York, 1993.

French Edition, 1995.

ORIGINAL RESEARCH AND REPORTS

1. Speroff L, Separation, location, and purification of antibody from rabbit serum using anion exchange chromatography, Thesis for M.D. Degree, Case Western Reserve University School of Medicine, 1961.

2. Speroff L, The bleeding corpus luteum, Obstet Gynecol 28:416-420, 1966.

3. Speroff L, Bacterial shock in obstetrics and gynecology, Am J Obstet Gynecol 95:139-151, 1966.

4. Speroff L, Davis CD, The management of bacterial shock and septic abortion, Connecticut Medicine 30:722-724, 1966.

5. Speroff L, Ramwell PW, Prostaglandin stimulation of in vitro progesterone synthesis, J Clin Endocrinol Metab 30:345-351, 1970.

6. Speroff L, Results of tubal surgery at the Columbia-Presbyterian Medical Center, Bull Sloane Hosp for Women 16:123-128, 1970.

7. Speroff L, Vande Wiele RL, Regulation of the human menstrual cycle, Am J Obstet Gynecol 109:234-250, 1971.

8. Anderson GG, Hobbins JC, Cordero L, Speroff L, Clinical use of prostaglandins and oxytocin substances, Ann New York Acad Sci 180:499-512, 1971.

9. Speroff L, Discussion of session on prostaglandins in female reproductive physiology, Ann New York Acad Sci 180:513-517, 1971.

10. Caldwell BV, Burstein S, Brock WA, Speroff L, Radioimmunoassay of F prostaglandins, J Clin Endocrinol Metab 33:171-175, 1971.

11. Speroff L, The effect of prostaglandin F_{2a} infusion on free steroid levels in early pregnancy, in Sobrero AJ, Harvey RM, editors, ADVANCES IN PLANNED PARENTHOOD, Vol VII, Excerpta Medica, Amsterdam, 1972, pp 151-154.

12. Anderson GG, Hobbins JC, Speroff L, Prostaglandins in the induction of labor, Am J Obstet Gynecol 112:382-386, 1972.

13. O'Grady JP, Caldwell BV, Auletta FJ, Speroff L, The effects of an inhibitor of prostaglandin synthesis (indomethacin) on ovulation, pregnancy, and pseudopregnancy in the rabbit, Prostaglandins 1:97-106, 1972.

14. Anderson GG, Hobbins JC, Rajkovic V, Caldwell BV, Speroff L, Midtrimester abortion using intraamniotic prostaglandin F_{2a}, Prostaglandins 1:147-156, 1972.

15. Anderson GG, Hobbins JC, Speroff L, Caldwell BV, The induction of therapeutic abortion using intravenous prostaglandins, Contraception 5:303-311, 1972.

16. O'Grady JP, Kohorn EL, Glass RH, Caldwell BV, Brock WA, Speroff L, Inhibition of in vitro progesterone synthesis by prostaglandin F_{2a}, J Reprod Fertil 30:153-156, 1972.

17. Engel T, Jewelewicz R, Dyrenfurth I, Speroff L, Vande Wiele RL, Ovarian hyperstimulation syndrome - a report of a case with notes on pathogenesis and treatment, Am J Obstet Gynecol 112:1052-1060, 1972.

18. Caldwell BV, Tillson SA, Brock WA, Speroff L, The effect of exogenous progesterone and estradiol on prostaglandin F levels in ovariectomized ewes, Prostaglandins 1:217-228, 1972.

19. Speroff L, Caldwell BV, Brock WA, Anderson GG, Hobbins JC, Hormone levels during prostaglandin F_{2a} infusions for therapeutic abortion, J Clin Endocrinol Metab 34:531-536, 1972.

20. Bogumil RJ, Ferin FM, Rootenberg J, Speroff L, Vande Wiele RL, Mathematical studies of the human menstrual cycle, J Clin Endocrinol Metab 35:126-143, 1972.

21. Hobbins JC, Brock WA, Speroff L, Anderson GG, Caldwell BV, Experience with the L/S ratio in predicting pulmonary maturity in utero, Obstet Gynecol 39:660-664, 1972.

22. Caldwell BV, Anderson GG, Hobbins JC, Speroff L, F prostaglandin levels in women receiving PGF_{2a} for therapeutic abortion, THE THIRD W.H.O. CONFERENCE ON PROSTAGLANDINS IN FERTILITY CONTROL, W.H.O. Research and Training Centre on Human Reproduction, Stockholm, 1972, pp 182-188.

23. Caldwell BV, Auletta FJ, Gordon JW, Speroff L, Further studies on the role of prostaglandins in reproductive physiology, THE THIRD W.H.0. CONFERENCE ON PROSTAGLANDINS IN FERTILITY CONTROL, W.H.O. Research and Training Centre on Human Reproduction, Stockholm, 1972, pp 217-233.

24. Zusman RM, Caldwell BV, Speroff L, Behrman HR, Radioimmunoassay of the A prostaglandins, Prostaglandins 1:41-53, 1972.

25. Anderson GG, Hobbins JC, Speroff L, Caldwell BV, Intravenous prostaglandins F_{2a} and E_2 and Syntocinon for the induction of term labor, fJ Reprod Med 9:287-291, 1972.

26. Caldwell BV, Speroff L, Brock WA, Auletta FJ, Gordon JW, Anderson GG, Hobbins JC, Development and application of a radioimmunoassay for F prostaglandins, J Reprod Med 9:361-371, 1972.

27. Anderson GG, Hobbins JC, Rajkovic V, Speroff L, Caldwell BV, Midtrimester abortion using intraamniotic prostaglandin F_{2a} with intravenous Syntocinon, J Reprod Med 9:434-436, 1972.

28. Yogman M, Speroff L, Huttenlocher PR, Kase NG, Child development after pregnancies complicated by low urinary estriol excretion and preeclampsia, Am J Obstet Gynecol 114:1069-1077, 1972.

29. Zusman RM, Spector D, Caldwell BV, Speroff L, Mulrow PJ, The effect of chronic sodium loading and sodium restriction on plasma prostaglandin A, E, and F concentration in normal humans, J Clin Invest 52:1093-1098, 1973.

30. Auletta FJ, Speroff L, Caldwell BV, Prostaglandin F_{2a} induced steroidogenesis and luteolysis in the primate corpus luteum, J Clin Endocrinol Metab 36:405-407, 1973.

31. Gore BZ, Caldwell BV, Speroff L, Estrogen-induced human luteolysis, J Clin Endocrinol Metab 36:615-617, 1973.

32. Larson JW, Hanson T, Caldwell BV, Speroff L, The effect of estradiol infusion on uterine activity and peripheral levels of F prostaglandins and progesterone, Am J Obstet Gynecol 117:276-279, 1973.

33. Speroff L, An essay: Prostaglandins and toxemia of pregnancy, Prostaglandins 3:721-728, 1973.

34. Anderson GG, Hobbins JC, Speroff L, Caldwell BV, The use of prostaglandins for the induction of labor, J Reprod Med 10:121-124, 1973.

35. Caldwell BV, Auletta FJ, Speroff L, Prostaglandins in the control of ovulation, corpus luteum function, and parturition, J Reprod Med 10:133-138, 1973.

36. Zusman RM, Forman BH, Schneider G, Caldwell BV, Speroff L, Mulrow PJ, The effect of chronic sodium loading and sodium restriction on plasma and renal concentrations of prostaglandin A in normal Wistar and spontaneously hypertensive AOKI rats, Clin Sci Molecular Med 45:325s-329s, 1973.

37. Zusman RM, Snider JJ, Cline A, Caldwell BV, Speroff L, Anti-hypertensive function of a renal carcinoma evidence for a prostaglandin secreting tumor, New Eng J Med 290:843-845, 1973.

38. Zusman RM, Spector D, Caldwell BV, Speroff L, Forman B, Schneider G, Mulrow PJ, Prostaglandin A concentration in plasma of normal and hypertensive humans, J Clin Invest 52:93a, 1973.

39. Spector D, Zusman RM, Caldwell BV, Speroff L, The distribution of prostaglandins A, E, and F in the human kidney, Prostaglandins 6:263-270, 1974.

40. Franklin GO, Dowd AJ, Caldwell BV, Speroff L, The effect of angiotensin-II intravenous infusion on plasma renin activity and prostaglandins A, E, and F levels in the uterine vein of the pregnant monkey, Prostaglandins 6:271-280, 1974.

41. Speroff L, Haning RV Jr, Ewaschuk EJ, Alberino SL, Kieliszek FX, Uterine artery blood flow studies in the pregnant monkey, in Lindheimer MD, Katz AL, Zuspan FP, editors, HYPERTENSION IN PREGNANCY, John Wiley & Sons, 1976, pp 315-327.

42. Ramey JN, Burrow GN, Spaulding SW, Donabedian RK, Speroff L, Frantz AG, The effect of aspirin and indomethacin on the TRH response in man, J Clin Endocrinol Metab 43:107-114, 1976.

43. Berger HJ, Zaret BL, Speroff L, Cohen LS, Wolfson S, Regional cardiac prostaglandin release during myocardial ischemia in anesthetized dogs, Circulation Res 38:566-571, 1976.

44. Auletta FJ, Caldwell BV, Speroff L, Estrogen-induced luteolysis in the Rhesus monkey: Reversal with indomethacin, Prostaglandins 11:745-752, 1976.

45. Berger JH, Speroff L, Wolfson S, Pentobarbital anesthesia: Lack of effect on venous prostaglandins in dogs, Prostaglandins 11:499-502, 1976.

46. Knox GE, Caldwell BV, Ziminski CM, Hoffman DC, Speroff L, Prevention of endotoxin induced death in rabbits with indomethacin, Clin Res 24:71A, 1976.

47. Berger HJ, Zaret BL, Speroff L, Cohen LS, Wolfson S, Cardiac prostaglandin release during myocardial ischemia induced by atrial pacing in patients with coronary artery disease, Am J Cardiology 39:481-486, 1977.

48. Haning RV Jr, Kielzek FX, Alberino SP, Speroff L, A radioimmunoassay for 13,14-dihydro-15-keto prostaglandin F_{2a} with chromatography and internal recovery standard, Prostaglandins 13:455-478, 1977.

49. Haning RV Jr, Satin KP, Lynskey MT, Speroff L, A direct radioimmunoassay for estriol-16-glucuronide in urine for monitoring pregnancy and induction of ovulation, Am J Obstet Gynecol 128:793-802, 1977.

50. Speroff L, Haning RV Jr, Levin R, The effect of angiotensin-II and indomethacin on uterine artery blood flow in the pregnant monkey, Obstet Gynecol 50:611-614, 1977.

51. Thliveris JA, Speroff L, Ultrastructure of the placental villi, chorion laeve and decidua parietalis in normal and hypertensive pregnancies, Am J Obstet Gynecol 129:492-498, 1977.

52. Haning RV Jr, Barrett DA, Alberino SP, Lynskey MT, Donabedian R, Speroff L, Interrelationships between maternal and cord prolactin, progesterone, estradiol, 13,14-dihydro-15-keto-prostaglandin F_{2a}, and cord cortisol at delivery with respect to initiation of parturition, Am J Obstet Gynecol 130:204-210, 1978.

53. Becker RA, Hayashi RH, Franks RC, Speroff, L, Effects of positional change and sodium balance on the renin-angiotensin-aldosterone system, big renin, and prostaglandins in normal pregnancy, J Clin Endocrinol Metab 46:467-472, 1978.

54. Gorlitsky GA, Kase NG, Speroff L, Ovulation and pregnancy rates with clomiphene citrate, Obstet Gynecol 51:256-296, 1978.

55. Haning RV Jr, Levin R, Behrman H, Kase NG, Speroff L, Plasma estradiol window and urinary estriol glucuronide determinations for monitoring menotropins induction of ovulation, Obstet Gynecol 54:442-447, 1979.

56. Speroff L, Levin R, Haning RV Jr, Kase NG, A practical approach for the evaluation of women with abnormal polytomography and elevated prolactin levels, Am J Obstet Gynecol 135:896-906, 1979.

57. Speroff L, Redwine DB, Exercise and menstrual function, The Physician and Sportsmedicine, 8:42-52, 1980.

58. Wagner JM, Morton MJ, Wagner JH, Johnson KA, O'Grady JP, Speroff L, Terbutaline and maternal cardiac function, JAMA 246:2697-2701, 1981.

59. Veille JC, Hohimer AR, Burry K, Speroff L, The effect of exercise on uterine activity in the last eight weeks of pregnancy, Am J Obstet Gynecol 151:727-730, 1985.

60. Veille JC, Morton MJ, Burry K, Nemeth M, Speroff L, Estradiol and hemodynamics during ovulation induction, J Clin Endocrinol Metab 63:721, 1986.

61. Speroff T, Dawson N, Speroff L, Is estrogen use for postmenopausal women too risky? Clin Res 35:362A, 1987.

62. Gordon MG, Williams SR, Frenchek B, Mazur CH, Speroff L, Dose-dependent effects of postmenopausal estrogen/progestin on antithrombin III and factor XII, J Lab Clin Med 111:52, 1988.

63. Williams SR, Rothchild I, Wesolowski D, Austin C, Speroff L, Does exposure of preovulatory oocytes to ultrasonic radiation affect reproductive potential? J In Vitro Fertiliz Embryo Transf 5:18, 1988.

64. Williams SR, Frenchek B, Speroff T, Speroff L, A study of combined continuous ethinyl estradiol and norethindrone acetate for postmenopausal hormone replacement, Am J Obstet Gynecol 162:438-436, 1990.

65. Speroff T, Dawson NV, Speroff L, Haber RJ, A risk-benefit analysis of elective bilateral oophorectomy: Effect of changes in compliance with estrogen therapy on outcome, Am J Obstet Gynecol 164:165-174, 1991.

66. Gonzalez F, Hatala DA, Speroff L, Basal and dynamic hormonal responses to gonadotropin releasing hormone agonist treatment in women with polycystic ovaries with high and low dehydroepiandrosterone sulfate levels, Am J Obstet Gynecol 165:535-545, 1991.

67. Hickok LR, Toomey C, Speroff L, A comparison of esterified estrogens with and without methyltestosterone: Effects on endometrial histology and serum lipoproteins in postmenopausal women, Obstet Gynecol 82:919-924, 1993.

68. Giraud GD, Morton MJ, Wilson RA, Burry KA, Speroff L, Effects of estrogen and progestin on aortic size and compliance in postmenopausal women, Am J Obstet Gynecol 174:1708-18, 1996.

69. Rosenberg MJ, Foldesy R, Mishell DR Jr, Speroff L, Waugh MS, Burkman R, Performance of the TCu380A and Cu-Fix IUDs in an intenational randomized trial, Contraception 53:197-03, 1996.

70. Speroff L, Rowan J, Symons J, Genant H, Wilborn W, for the CHART Study Group, The compa hormones as replacement therapy (CHART Study), JAMA 276:1397-03, 1996.

71. Speroff L, Whitcomb RW, Kempfert NJ, Boyd RA, Paulissen JB, Rowan JP, Effecacy and local tolerance of a low-dose 7-day matrix estradiol transdermal delivery system in the treatment of menopausal vasomotor symptoms, Obstet Gynecol 88:587-92, 1996.

72. Symons J, Kempfert N, Speroff L, for the FemHRT Study Investigators, Vaginal bleeding in postmenopausal women taking low-dose norethindrone acetate and ethinyl estradiol combinations, Obstet Gynecol 96:366-72, 2000.

73. Speroff L, Symons J, Kempfert N, Rowan J, for the femhrt Study Investigators, The effect of varying low dose combinations of norethindrone aceate and ethinyl estradiol (femhrt) on the frequency and intensity of vasomotor symptoms, Menopause 7:383-90, 2000.

73. Pickar JH, Yeh I-T, Wheeler JE, Cunnane MF, Speroff L, Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate, Fertil Steril 76:25-31, 2001.

74. Simon JA, Liu JH, Speroff L, Shumel BS, Symons JP, Reduced vaginal bleeding in postmenopausal women taking combined norethindrone acetate and low-dose ethinyl estradiol versus combined conjugated equine estrogens and medroxyprogesterone acetate, Am J Obstet Gynecol 188:92-99, 2003.

75. Speroff L, for the United States VR Investigator Group, Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms, Obstet Gynecol 102:823-834, 2003

76. LaGuardia KD, Shangold G, Fisher A, Friedman A, Kafrissen M, the Noregestimate Study Group, Efficacy, safety and cycle control of five oral contraceptive regimens containing norgestimate and ethinyl estradiol, Contraception 67:431-437, 2003.

77. Pickar JH, Yeh I-T, Wheeler JE, Cunnane MF, Speroff L, Endometrial effects of lower doses of conjugated estrogens and medroxyprogesterone acetate: two-year substudy results, Fertil Steril 80:1234-1240, 2003.

78. Sonnenberg FA, Burkman R, Hagerty CG, Speroff L, Speroff T, Costs and net health effects of contraceptive methods, Contraception 69:447-459, 2004.

79. Sonnenberg FA, Burkman RT, Speroff L, Westhoff C, Hagerty CG, Cost-effectiveness and contraceptive effectiveness of the transdermal contraceptive patch, Am J Obstet Gynecol 192:1-9, 2005.

80. Utian WH, Speroff L, Ellman H, Dart C, Comparative controlled trial of a novel oral estrogen therapy, estradiol acetate, for relief of menopause symptoms, Menopause 12:708-715, 2005.

81. Speroff L, Haney AF, Gilbert RD, Ellman H, for the Estradiol Acetate Investigator Group, Efficacy of a new, oral estradiol acetate formulation for relief of menopausal symptoms, Menopause 13:442-450, 2006.

82. Rowan J, Simon JA, Speroff L, Ellman H, Effects of low-dose norethindrone acetate plus ethinyl estradiol (o.5 mg/2.5 µg) in women with postmenopausal symptoms: updated analysis of three randomized controlled trials, Clin Therap 28:921-932, 2006.

83. Speroff L, A clinical profile of 24-day oral contraceptives, Expert Review of Obstetrics and Gynecology, 2:367-370, 2007.

84. Speroff L, The future of postmenopausal hormone therapy: It's time to move forward, Maturitas 57:103-106, 2007.

85. Speroff L, Gass M, Constantine G, Olivier S, for the Study 315 Investigators, Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms, Obstet Gynecol 111:77-87, 2008

86. Speroff L, Postmenopausal hormone therapy and the risk of breast cancer. A contrary thought, Menopause 15:393-400, 2008.

87. Ellinas SP, Trokoudes K, Ellinas PA, Speroff L, Successful pregnancy by fresh-embryo donor IVF post leukemia, bone marrow transplantation and chemotherapy-induced amenorrhea, Obstet Gynecol, submitted.

88. Kaunitz AM, Darney PD, Ross D, Wolter K, Speroff L, Subcutaneious depot medroxyprogesterone acetate (DMPA) versus intramuscular DMPA: a 3-year randomized study of contraceptive efficacy, safety and user satisfaction, submitted.

89. Pickar JH, Yeh I-T, Bachmann G, Speroff L, A new approach to endometrial protection in menopausal therapy with a tissue selective estrogen complex (TSEC) containing bazedoxifene/conjugated estrogens (BZA/CE): a randomized, controlled trial, submitted.

BOOK CHAPTERS, REVIEWS, MISCELLANEOUS

1. Speroff L, The adrenogenital syndrome and its obstetrical aspects, Obstet Gynecol Survey 20:185-214, 1965.

2. Speroff L, Toxemia and the renin-angiotensin system, Bull Sloane Hospital for Women, 16:33-48, 1970.

3. Speroff L, Ramwell PW, Prostaglandins in reproductive physiology, Am J Obstet Gynecol 107:111-130, 1970.

4. Speroff L, Relationship of prostaglandins to reproductive function, Bull Sloane Hospital for Women, 16:117-122, 1970.

5. Anderson GG, Speroff L, Prostaglandins and abortion, Clin Obstet Gynecol 14:245-257, 1971.

6. Speroff L, The clinical use of prostaglandins, Drugs of Today, 7:815, 1971.

7. Anderson GG, Speroff L, Prostaglandins, Science 171:502-504, 1971.

8. Speroff L, The prostaglandins - Enthusiasm and caution in equal doses, Hospital Practice, Feb., 1971.

9. Caldwell BV, Brock WA, Gordon JW, Speroff L, Some practical considerations in the radioimmunoassay of F prostaglandins, THE THIRD W.H.O. CONFERENCE ON PROSTAGLANDINS IN FERTILITY CONTROL, W.H.O. Research and Training Centre on Human Reproduction, Stockholm, 1972, pp 83-91.

10. Anderson GG, Speroff L, Clinical uses of prostaglandins in reproduction, in Ramwell PW, Pharriss BB, editors, PROSTAGLANDINS, Plenum Press, New York, 1973, pp 361-382.

11. Speroff L, Anderson GG, Prostaglandins and fertility control, in Hafez ESE, Evans TN, editors, HUMAN REPRODUCTION, Harper and Row, Hagerstown, Maryland, 1973, pp 361-382.

12. Speroff L, Prostaglandins and abortion, in Osofsky HJ, Osofsky JD, editors, ABORTION EXPERIENCE IN THE UNITED STATES, Harper and Row, Hagerstown, Maryland, 1973, pp 415-435.

13. Speroff L, Physiologic and pharmacologic roles for prostaglandins in obstetrics, Clin Obstet Gynecol 16:109-129, 1973.

14. Speroff L, Brenner WE, Spellacy WN, Anderson GG, Csapo AA, A report on prostaglandins for abortion, Contemporary OB/GYN, 2:83-108, 1973.

15. Speroff L, Toxemia of pregnancy, Mechanism and therapeutic management, Am J Cardiology 32:582-591, 1973, and in Laragh JH, editor, HYPERTENSION MANUAL, Yorke Medical Books, New York, 1974, pp 441-460.

16. Speroff L, Anovulation and hirsutism, Contemporary OB/GYN 4:45-50, 1974.

17. Kase NG, Speroff L, the Ovary, in Bondy PD, Rosenberg LS, editors, DUNCAN'S DISEASES OF METABOLISM, W.B. Saunders, 1974, pp 1585-1628.

18. Speroff L, The problem of obesity, Contemporary OB/GYN 5:85-90, 1975.

19. Speroff L, Workup and treatment of hirsutism, Audio-Digest, 1975.

20. Speroff L, Management of amenorrhea, Audio/Scope, 1975.

21. Anderson GG, Hobbins JC, Speroff L, The high risk patient, in Burrow GN, Ferris TF, editors, MEDICAL COMPLICATIONS DURING PREGNANCY, W.B. Saunders, 1975.

22. Speroff L, An autoregulatory role for prostaglandins in placental hemodynamics, their possible influence on blood pressure in pregnancy, J Reprod Med 15:181-188, 1975.

23. Speroff L, The endocrinology of parturition, Mead Johnson Symposium on Perinatal and Developmental Medicine, December, 1976.

24. Speroff L, A homeostatic mechanism for regulation of uteroplacental blood flow, Mead Johnson Symposium on Perinatal and Developmental Medicine, December, 1976.

25. Speroff L, Prostaglandins and fertility control, in Moghissi KS, Evans TN, editors, REGULATION OF HUMAN FERTILITY, Wayne State University Press, 1976, pp 144-163.

26. Speroff L, Amenorrhea, in Glass RH, editor, OFFICE GYNECOLOGY, Williams & Wilkins, Baltimore, 1976, pp 227-239.

27. Speroff L, Which birth control pill should be prescribed? Fertil Steril 27:997-1008, 1976.

28. Speroff L, Kase NG, Basic endocrinological principles of the sex steroids, in Simpson JL, DISORDERS OF SEXUAL DIFFERENTIATION, Academic Press Inc, 1976, pp 112-140.

29. Speroff L, Hypertension in pregnancy: Role of prostaglandins? Contemporary OB/GYN 7:27-30, 1976.

30. Speroff L, Archer DF, Berger MJ, Tredway DR, Workup on menstrual irregularities, Contemporary OB/GYN 7:132-181, 1976.

31. Speroff L, What initiates labor? Contemporary OB/GYN 7:113-121, 1976.

32. Speroff L, Judd HL, Richart RM, Ziel HK, The estrogen replacement controversy, Contemporary OB/GYN 8:143-178, 1976.

33. Speroff L, Anovulation and hirsutism, in de Alvarez RR, editor, TEXTBOOK OF GYNECOLOGY, Lea and Febiger, 1977, pp 135-146.

34. Speroff L, Hormonal events and disorders of the menstrual cycle, in Givens J, editor, GYNECOLOGIC ENDOCRINOLOGY, Yearbook, 1977, pp 21-33.

35. Speroff L, Office management of hirsutism, Female Patient 3:27-30, 1977.

36. Speroff L, Dorfman GS, Prostaglandins and pregnancy hypertension, Clinics in Obstet Gynecol 4:635-649, 1977.

37. Speroff L, Becker RA, Gant NF, Pregnancy-induced hypertension, Contemporary OB/GYN 9:137-160, 1977.

38. Speroff L, The breast as an endocrine target organ, Contemporary OB/GYN 9:69-72, May, 1977.

39. Speroff L, Alexander NJ, Novy MJ, Techniques of artificial insemination, Contemporary OB/GYN 9:-63-88, June, 1977.

40. Speroff L, Isolating the cause of amenorrhea, Contemporary OB/GYN 10:113-122, September, 1977.

41. Speroff L, Berger G, Palomaki JF, Yuzpe A, Clinical problems with oral contraceptives, Contemporary OB/GYN 10:114-152, October, 1977.

42. Speroff L, Jewelewicz R, L'Hermite M, Marshall JR, Treating the patient who doesn't ovulate, Contemporary OB/GYN 12:121-149, July, 1978.

43. Speroff L, Is there a biologic basis for homosexuality? Contemporary OB/GYN 12:65-74, August, 1978.

44. Speroff L, Important clinical roles for steroid hormone receptors, Contemporary OB/GYN 12:99-104, October, 1978.

45. Speroff L, Human ovarian steroidogenesis, morphology, and function, in Caplan RM, Sweeney WJ, editors, ADVANCES IN OBSTETRICS AND GYNECOLOGY, Williams & Wilkins, Baltimore, 1978, pp 375-386.

46. Speroff L, Estrogen and progestin therapy for reasons other than contraception, in Diamond MC, Korenbret CC, editors, HORMONAL CONTRACEPTIVES, ESTROGENS, AND HUMAN WELFARE, Academic Press, New York, 1978, pp 15-29.

47. Speroff L, Normal and abnormal menstruation, in Benson R, CURRENT OBSTETRIC AND GYNECOLOGIC DIAGNOSIS AND TREATMENT, Lange Medical Publications, Los Altos, 1978, pp 102-126.

48. Speroff L, Davidson J, Fisk N, The clinician and the homosexual patient, Contemporary OB/GYN 14:92-107, August, 1979.

49. Speroff L, Cunningham G, Lipschultz LI, Paulson DF, Infertility in men: What the gynecologist needs to know, Contemporary OB/GYN 14:188-208, September, 1979.

50. Speroff L, Which birth control pill should be prescribed? in Wallach EE, Kempers RD, editors, MODERN TRENDS IN INFERTILITY AND CONCEPTION CONTROL, Williams & Wilkins, Baltimore, 1979, pp 374-391.

51. Speroff L, Prostaglandins in pregnancy: Effects on the fetus and the newborn, in Nitzan M, editor, THE INFLUENCE OF MATERNAL HORMONES ON THE FETUS AND NEWBORN, Pediatric and Adolescent Endocrinology, Vol 5, S. Karger, 1979, pp 167-176.

52. Speroff L, Oral contraceptives: Low dose versus high dose estrogen, in Moghissi KS, editor, CONTROVERSIES IN CONTRACEPTION, Williams & Wilkins, Baltimore, 1979, pp 167-176.

53. Speroff L, Baramaki TA, Riddick D, Stone SC, Solving the riddles of amenorrhea, Contemporary OB/GYN 15:48-83, March, 1980.

54. Speroff L, Editorial comment, Contemporary OB/GYN 15:43, June, 1980.

55. Speroff L, Untangling reproductive neuroendocrinology, Contemporary OB/GYN 16:44-68, July, 1980.

56. Kase NG, Speroff L, The ovary, in Bondy PK, Rosenberg LS, editors, METABOLIC CONTROL AND DISEASE, W.B. Saunders, Philadelphia, 1980, pp 1579-1612.

57. Speroff L, Which birth control pill is the best? Postgraduate Obstet Gynecol, Vol 1, No. 12, July, 1980.

58. Speroff L, The case for prophylactic oophorectomy, Postgraduate Obstet Gynecol, Vol 1, No. 14, August, 1980.

59. Speroff L, Can exercise cause problems in pregnancy and menstruation? Contemporary OB/GYN 16:5770, September, 1980.

60. Speroff L, Normal and abnormal menstruation, in Benson R, CURRENT OBSTETRICS AND GYNECOLOGIC DIAGNOSIS AND TREATMENT, Lange Medical Publications, Los Altos, 1980.

61. Speroff L, The polycystic ovary, Postgraduate Obstet Gynecol, Vol 1, No. 21, November, 1980.

62. Speroff L, Riddick DH, Worley RJ, Guide to using the lab for common endocrine tests, Contemporary OB/GYN 17:168-178, January, 1981.

63. Speroff L, Hirsutism: Evaluation and management, Slidecassette AV package, American College of Obstetricians and Gynecologists, 1981.

64. Speroff L, The ovary, in Felig P, Baxter JD, Broadus A, Frohman LA, editors, ENDOCRINOLOGY AND METABOLISM, McGraw-Hill, 1981.

65. Speroff L, A brief for low-dose pills, Contemporary OB/GYN 17:2732, May, 1981.

66. Speroff L, Managing galactorrhea in pill patients, Contraceptive Technology 2:81, 1981.

67. Speroff L, Managing anovulatory bleeding medically, Contemporary OB/GYN 18:121-124, July, 1981.

68. Speroff L, Getting high on running, Fertil Steril 36:149-151, 1981.

69. Speroff L, Amenorrhea, in Glass RH, editor, OFFICE GYNECOLOGY, Williams & Wilkins, Baltimore, 2nd edition, 1981.

70. Speroff L, Managing anovulatory bleeding medically, in Queenan JT, editor, MANAGING OB/GYN EMERGENCIES, Medical Economics Inc, New Jersey, 1982.

71. Speroff L, The premenstrual syndrome: A challenge to the science and art of medicine, Contemporary OB/GYN 19:15-17, May, 1982.

72. Speroff L, Exercise, in Queenan JT, Hobbins JC, editors, PROTOCOLS FOR HIGH RISK PREGNANCIES, Medical Economics Books, New Jersey, 1982, pp 10-13.

73. Speroff L, Toward a new style of leadership in ob/gyn, Contemporary OB/GYN 19:147-166, June, 1982.

74. Speroff L, Exercise and pregnancy, Postgraduate Obstet Gynecol, Vol 2, No. 12, June, 1982.

75. Speroff L, The formulation of birth control pills. Does it make a clinical difference? Johns Hopkins Med J 150:170, 1982.

76. Fritz MA, Speroff L, The endocrinology of the menstrual cycle: The interaction of folliculogenesis and neuroendocrine mechanisms, Fertil Steril 38:509-529, 1982.

77. Speroff L, Avoiding the pitfalls of infertility management, Contemporary OB/GYN, January, 1983, pp 127-141.

78. Speroff L, editor, Menopause, Seminars Reprod Endocrinol, Vol 1, No. 1, 1983.

79. Speroff L, Archer DF, Bates GW, Grimes E, When and how should you use bromocriptine, Contemporary OB/GYN, March, 1983, pp 97-135.

80. Speroff L, Anovulatory bleeding, in Queenan J, editor, MANAGING OB/GYN EMERGENCIES, Medical Economic Books, New Jersey, 1983, pp 214-218.

81. Speroff L, How hormones work, Postgraduate Obstet Gynecol, Vol 3, No. 6, March, 1983.

82. Fritz MA, Speroff L, The role of progestational agents in hormone replacement therapy, in Buchsbaum HJ, editor, THE MENOPAUSE, Springer-Verlag, New York, 1983.

83. Speroff L, Contraception for adolescents, Postgraduate Obstet Gynecol, Vol 3, No. 14, July, 1983.

84. Speroff L, PMS - looking for new answers to an old problem, Contemporary OB/GYN, August, 1983, pp 102-203.

85. Speroff L, Riddick DH, Worley r, How to induce ovulation, Contemporary OB/GYN, October, 1983, pp 199-214.

86. Speroff L, Marijuana and health, Postgraduate Obstet Gynecol, Vol 3, No. 25, December, 1983.

87. Speroff L, The effect of exercise on the menstrual cycle, Postgraduate Obstet Gynecol, Vol 4, No. 4, February, 1984.

88. Speroff L, Keye W, Steege J, Helping your patients cope with PMS, Contemporary OB/GYN, April, 1984, pp 165-190.

89. DeFazio J, Speroff L, Preoperative and postoperative management of the patient undergoing infertility surgery, Seminars Reprod Endocrinol 2:102-109, 1984.

90. Austin CM, Speroff L, Drugs for use in infertility, Postgraduate Obstet Gynecol, Vol 4, No. 18, August, 1984.

91. Budoff PN, Darney PD, Speroff L, Kaiser HB, Prescribing oral contraceptives in 1985, Patient Care 19:16, 1985.

92. DeFazio J, Austin C, Speroff L, Pathophysiologic basis for the menopause, Adv Psychosom Med 12:25-35, 1985.

93. DeFazio J, Speroff L, Ultrasonography's role in infertility, Contemporary OB/GYN, June, 1985, pp 194-205.

94. Speroff L, Why mammography is effective, Contemporary OB/GYN, September, 1985, pp 183-190.

95. Speroff L, Gelfand M, Gibbons WA, Richart RM, Adding progestogens to estrogen replacement therapy, Contemporary OB/GYN, September, 1985, pp 225-242.

96. Evans JA, Austin CM, Speroff L, The GnRH pump in the induction of ovulation, Postgraduate Obstet Gynecol, Vol 5, No. 24, November, 1985.

97. DeFazio J, Speroff L, Estrogen replacement therapy, current thinking and practice, Geriatrics 40:32-47, 1985.

98. Speroff L, Grimes DA, Mishell DR Jr, Quagliarello J, Prescribing OC's for safety, Contemporary OB/GYN, March, 1986, pp 128-148.

99. Speroff L, Fagan P, Rosenthal M, Smith D, Sexuality in older women, Contemporary OB/GYN, April, 1986, pp 212-228.

100. Speroff L, editor, Oral contraception, 1986: Investigating the issues, J Reprod Med, Vol 31, June, 1986.

101. Speroff L, Update on estrogen-progestin replacement therapy, Postgraduate Obstet Gynecol, Vol 6, No. 24, November, 1986.

102. Speroff L, Estrogen replacement today: A preventive health care issue, CURRENT TRENDS IN ESTROGEN REPLACEMENT THERAPY, HP Publishing Company, 1986.

103. Speroff L, Stress, weight, and reproduction, in Riddick DH, editor, REPRODUCTIVE PHYSIOLOGY IN CLINICAL PRACTICE, Thieme Medical Publishers Inc, New York, 1987, pp 71-80.

104. Speroff L, To use progestin or not, Contemporary OB/GYN, February, 1987, pp 13-15.

105. Speroff L, Which birth control pill should be prescribed today? Contemporary OB/GYN, March, 1987, pp 102-124.

106. Speroff L, Meldrum DR, Stumpf PG, Whitehead M, ERT - whom to treat and how, Contemporary OB/GYN, April, 1987, pp 179-193.

107. Williams S, Speroff L, Dance and menstrual function, in Ryan A, Stevens R, editors, DANCE MEDICINE, Pluribus Press Inc, 1987.

108. Speroff L, Wallach EE, The changing face of infertility, Contemporary OB/GYN, September, 1987, pp 8-23.

109. Speroff L, Recognition and management of anorexia nervosa, Your Patient & Fitness 1:6-10, 1987.

110. Russell KP, Frankl G, Speroff L, Screening and early diagnosis of breast cancer, Audiocassette, American College of Obstetricians and Gynecologists, 1987.

111. Speroff L, Amenorrhea, in Glass RH, editor, OFFICE GYNECOLOGY, Williams & Wilkins, Baltimore, 3rd edition, 1988, pp 231-250.

112. Kanaan C, Speroff L, Diabetes mellitus in pregnancy, Postgraduate Obstet Gynecol, Vol 8, No. 2, January, 1988.

113. Speroff L, Sperm enhancement, Postgraduate Obstet Gynecol, Vol 8, No. 4, February, 1988.

114. Speroff L, Haney AF, Lobo RA, Schiff I, Options in estrogen replacement therapy, Contemporary OB/GYN, March, 1988, pp 190-210.

115. Speroff L, Breast cancer: A perspective and overview of epidemiologic information and of the current studies of detection and mortality, Video J Obstet Gynecol, Vol 1, No. 1, March, 1988.

116. Speroff L, Special issue editor, THE WOMAN OVER 50, Contemporary OB/GYN, April 15, 1988.

117. Speroff L, The woman over 50: A new challenge for the gynecologist, Contemporary OB/GYN, April 15, 1988, pp 22-40.

118. Speroff L, Some observations on the progestational component in hormone replacement therapy, Contemporary OB/GYN, April 15, 1988, pp 61-64.

119. Speroff L, PMS: Historical and social perspectives, in Keye WR Jr, editor, THE PREMENSTRUAL SYNDROME, W.B. Saunders Company, Philadelphia, 1988, pp 2-14.

120. Speroff L, A review of the cholesterol profile, Postgraduate Obstet Gynecol, Vol. 8, No. 13, June, 1988.

121. Speroff L, Peptides involved in the regulation of the menstrual cycle, Postgraduate Obstet Gynecol, Vol. 8, No. 14, July, 1988.

122. Speroff L, Archer DF, Mishell DR Jr, Multiphasic and monophasic OCs: Is there a difference? Contemporary OB/GYN, Sept 15, 1988, pp 124-145.

123. Omodei U, Speroff L, Outlook on continuous estrogen-progestin therapy, Contemporary OB/GYN, Sept 15, 1988, pp 171-195.

124. Speroff L, Bush T, Castelli WP, Stampfer M, How ERT influences cardiovascular disease, Contemporary OB/GYN, November, 1988, pp 108-129.

125. Speroff L, RU 486: Political controversy over clinical potential, Postgraduate Obstet Gynecol, Vol 8, No. 24. December, 1988.

126. Speroff L, The urinary tract in elderly women - Part I, Postgraduate Obstet Gynecol, Vol. 9, No. 2, January, 1989.

127. Speroff L, The urinary tract in elderly women - Part II, Postgraduate Obstet Gynecol, Vol. 9, No. 3, February, 1989.

128. Speroff L, Haney AF, Moore D, Plan ML, Exploring superovulation for infertile patients, Contemporary OB/GYN, March, 1989, pp 128-160.

129. Speroff L, Hatasaka H, Breast disease in the mature woman, Obstet Gynecol Forum 3:2, 1989.

130. Speroff L, Should older women use oral contraceptives? Contemporary OB/GYN, November, 1989, pp 15-16,160.

131. Speroff L, From OCs to replacement therapy: A strategy for transition, Dialogues in Contraception, Vol. 2, No. 8, Fall, 1989.

132. Speroff L, Menopause & Good Health, Parts 1,2, & 3, Video Tapes, 1989.

133. Cohen I, Speroff L, Ovarian hyperstimulation syndrome, Postgraduate Obstet Gynecol, Vol. 10, No. 2, January, 1990.

134. Speroff L, Breast cancer and postmenopausal hormone therapy, Contemporary OB/GYN, January, 1990, pp 71-82.

135. Speroff L, Screening for thyroid disease in older women, Postgraduate Obstet Gynecol, Vol 10, No. 11, May, 1990.

136. Mishell DR Jr, Connell C, Haney A, Hodgen G, Speroff L, Oral contraception for women in their 40s, J Reprod Med 35:No. 4 (Supplement), 1990.

137. Gonzalez F, Speroff, L, Adrenal morphologic considerations in polycystic ovary syndrome, Obstet Gynec Survery 45:491-508, 1990.

138. Speroff L, Male infertility - intrauterine insemination, in Quilligan E, Zuspan F, editors, CURRENT THERAPY IN OBSTETRICS AND GYNECOLOGY, 3rd edition, W.B. Saunders Co., Philadelphia, 1990, pp 78-80.

139. Speroff L, A physician's approach to sexuality and aging, Postgraduate Obstet Gynecol, Vol. 10, No. 17, August, 1990.

140. Speroff L, Friedman A, Wolf DP, Who benefits from intrauterine insemination with washed sperm? Contemporary OB/GYN, October, 1990, pp 65-77.

141. Speroff L, Cardiovascular disease and postmenopausal hormone replacement therapy, The Endocrinologist 1:49-56, 1991.

142. Speroff L, Hirsutism: Evaluation and management, Slidecassette AV package, American College of Obstetricians and Gynecologists, 1991.

143. Cohen I, Speroff L, Premature ovarian failure: Update, Obstet Gynecol Survey 46:156-162, 1991.

144. Speroff L, Cardiovascular disease and osteoporosis: Combined estrogen-progestin postmenopausal hormone replacement therapy, Video J Obstet Gynec IV: No. 2, March, 1991.

145. Speroff, L, Haney, A, Lippman M, Schlesselman J, Role of hormones in breast cancer risk, Contemporary OB/GYN April, 1991, pp 80-95.

146. Speroff L, A clinician's approach to therapy during a woman's tansition years, Contemporary OB/GYN, August, 1991, pp 64-68.

147. Hickock L, Speroff L, The Menopause, in Conn RB, CURRENT DIAGNOSIS, W.B. Saunders Company, Philadelphia, 1991, pp 1202-1205.

148. Speroff L, Anorexia, bulimia, and pregnancy, in O'Grady JP, Rosenthal M, editors, OBSTETRICS: PSYCHOLOGICAL AND PSYCHIATRIC SYNDROMES, Elsevier, New York, 1992, pp 151-162.

149. Hickock LR, Speroff L, Estrogen-Progestin Replacement Therapy, in Rayburn WF, Zuspan FP, editors, DRUG THERAPY IN OBSTETRICS AND GYNECOLOGY, Mosby Year Book, Inc., St Louis, 1992, pp 526-541.

150. Darney PD, Grimes D, Speroff L, Long-acting contraception, ACOG Update, Vol. 17, 1992.

151. Speroff L, Parker-Jones K, Davis A, Compliance problems with OCs and HRT, Contemporary OB/GYN, April, 1992, pp 88-110.

152. Hickok LR, Speroff L, The role of growth factors in ovarian physiology, Postgraduate Obstet Gynecol, Vol 12, No 11, May, 1992.

153. Speroff L, The risk of breast cancer associated with oral contraception and hormone replacment therapy, Womens' Health Issues 2:63-72, 1992.

154. Speroff L, Special issue editor, Editorial: Breast cancer: a concern and obligation for all, Breast Health 1992, Contemporary OB/GYN, June 15, 1992.

155. Speroff L, Tamoxifen: special considerations for gynecologists, Contemporary OB/GYN, June 15, 1992, pp 50-61.

156. Speroff L, Breastfeeding and contraception, Postgraduate Obstet Gynecol, Vol 12, No. 12, June, 1992.

157. Speroff L, Contraception in the U.S.A., Postgraduate Obstet Gynecol, Vol 12, No. 10, September, 1992.

158. Hulka B, Lindsay R, Speroff L, Stampfer MJ, Singer K, Hormone replacement therapy: what risks? Contemporary OB/GYN, November, 1992, pp 90-130.

159. Speroff L, Menopause and hormone replacement therapy, in Kaiser F, editor, CLINICS IN GERIATRIC MEDICINE, Vol. 9, Feb. 1993, pp 33-56.

160. Speroff L, Controversial issues in menopausal management, in Mishell DR Jr, editor, 1993 YEARBOOK IN OBSTETRICS AND GYNECOLOGY, Yearbook Publishers, Inc., 1993.

161. Speroff L, Jones KP, Kaunitz A, Schmidt P, Treating the perimenopausal patient, Contemporary OB/GYN, May, 1993, pp 124-140.

162. Speroff L, DeCherney A, Evaluation of a new generation of oral contraceptives, Obstet Gynecol 81:1034, 1993.

163. Speroff L, Amenorrhea, in Glass RH, editor, OFFICE GYNECOLOGY, Williams & Wilkins, Baltimore, 4th edition, 1993.

164. Speroff L, Ovarian follicular development is different in the primate, Postgraduate Obstet Gynecol, Vol. 13, No. 13, June, 1993.

165. Speroff L, HRT for the woman who has had breast Ca? Contemporary OB/GYN, July, 1993, pp 33-66.

166. Grimes DA, Mishell DR Jr, Speroff L, editors, Contraceptive choices for women with medical problems, Am J Obstet Gynecol, Vol. 168, June, 1993, Part 2.

167. Speroff L, Aging and reproduction, Postgraduate Obstet Gynecol, Vol. 13, No. 16, August, 1993.

168. Wenger NK, Speroff L, Packard B, Cardiovascular health and disease in women, New Engl J Med 329:247-256, 1993.

169. Speroff L, The impact of oral contraception and hormone replacement therapy on cardiovascular disease, in Wenger NK, Speroff L, Packard B, editors, CARDIOVASCULAR HEALTH AND DISEASE IN WOMEN, LeJacq Communications, Inc., 1993, pp 37-46.

170. Wenger NK, Speroff L, Packard B, editors, CARDIOVASCULAR HEALTH AND DISEASE IN WOMEN, LeJacq Communications, Inc., Greenwich, Connecticut, 1993.

171. Speroff L, Which oral contraceptive pill should be prescribed? in Shoupe D, Haseltine FP, editors, CONTRACEPTION, Springer-Verlag, New York, 1993, pp 112-122.

172. Speroff L, The uterus is an endocrine organ, Postgraduate Obstet Gynecol, Vol 13, No. 25, December, 1993.

173. Speroff L, The menopause: A signal for the future, in Lobo RA, editor, TREATMENT OF THE POSTMENOPAUSAL WOMAN, Raven Press, New York, 1994, pp 1-8.

174. Speroff L, Normal and abnormal thyroid function in women, Postgraduate Obstet Gynecol, Vol 14, No. 5, February, 1994.

175. Speroff L, The effect of aging on fertility, Curr Opinion Obstet Gynecol 6:115-120, 1994.

176. Lobo RA, Speroff L, International consensus conference on postmenopausal hormone therapy and the cardiovascular system, Fertil Steril 61:592-595, 1994, and Heart Disease and Stroke 3:173-176, 1994.

177. Speroff L, Important protein messengers in pregnancy, Postgraduate Obstet Gynecol, vol 14, No. 9, April, 1994.

178. Speroff L, Soranus of Ephesus, The Endocrinologist 4:230-232, 1994.

179. Speroff L, Menopause, in Quilligan E, Zuspan F, editors, CURRENT THERAPY IN OBSTETRICS AND GYNECOLOGY, 4th edition, W.B. Saunders Co., Philadelphia, 1994, pp 87-91.

180. Speroff L, Premature ovarian failure, Advances in Endocrinol Metab, 6:233-258, 1995.

181. Speroff L, "Goody" was a great man: Gregory Goodwin Pincus (1903-1967), The Endocrinologist 5:249-252, 1995.

182. Andrews WC, Hammond CB, Speroff L, Menopause — emerging issues, ACOG Update, Vol 21, No. 3, 1995.

183. Speroff L, Haney AF, Jones KP, Treating patients during the transitional years, Contemporary OB/GYN, October, 1995, pp 83-98.

184. Speroff L, The perimenopausal transition: maximizing preventive health care, Womens' Health Reports 1:101-112, 1995.

185. Speroff L, Managing bleeding during postmenopausal hormone therapy, Womens' Health Reports 1:121-128, 1995.

186. Speroff L, editor, Menopause management, Excerpta Medica, Inc., 1995.

187. Speroff, Bush TL, Ettinger B, Lobo RA, Mishell DR Jr, New concepts in managing menopause: symposium, Medical Economics, Montvale, NJ, 1995.

188. Speroff L, Haney AF, Parker-Jones K, Preventive care during the transitional years, Contemporary OB/GYN, January, 1996, pp 95-100.

189. Speroff L, Hormonal contraception, in Adashi EY, Rock JA, Rosenwaks Z, editors, *Reproductive Endocrinology, Surgery, and Technology, Volume 2,* Lippincott-Raven Publishers, Philadelphia-New York, 1996, pp 1683-1708

190. Speroff L, Postmenopausal hormone therapy and breast cancer, Obstet Gynecol 87 (Suppl):44S-54S, 1996.

191. Speroff L, editor, Long- and short-term effects of exercise on women, Medical Economics, 1996.

192. Speroff L, The case for postmenopausal hormone therapy, Hospital Practice 31:75-89, 1996.

193. Henrich JB, Levinson W, Speroff L, The clinical management of abnormal menstruation, in Noble J, editor-in-chief, *Textbook of Primary Care Medicine,* Mosby-Year book, Inc, St. Louis, 1996, pp 1816-1824.

194. Speroff L, Shaw JC, Hirsutism and hyperandrogenism in women, in Noble J, editor-in-chief, *Textbook of Primary Care Medicine,* Mosby-Year book, Inc, St.Louis, 1996, pp 1824-1826.

195. Speroff L, Preventive health care for older women, Internat J Fertil Menopausal Studies 41:64-68, 1996.

196. Speroff L, Oral contraceptives and venous thromboembolism, Int J Gynecol Obstet 54:45-50, 1996.

197. Speroff L, Monograph 208: Midlife health care for women, AAFP Home Study Self-Assessment, American Academy of Family Physicians, 1996, pp 1-49.

198. Speroff L, The effect of oestrogen-progestogen postmenopausal hormone replacement therapy on the cardiovascular system, Eur Menopause J 3(Suppl):151-63, 1996.

199. Speroff L, Darney PD, Kaunitz AM, Mishell Dr Jr, Sulak PJ, Westhoff CL, Current clinical issues in oral contraception, Contemporary OB/GYN, Supplement to December, 1996, pp 3-44.

200. Speroff L, Assessment of the magnitude of the risk of breast cancer, J Clin Endocrinol Metab 81:3835-36, 1996.

201. Speroff L, Calle EE, Hankinson SE, Johnson CA, Weiss NS, Postmenopausal hormone therapy and breast cancer, Contemporary OB/GYN, Supplement to January, 1997, pp 4-30.

202. Speroff L, Collins P, Mishell DR Jr, Stampfer MJ, Sullivan JM, Postmenopausal hormone therapy and the cardiovascular system, Contemporary OB/GYN, Supplement to June, 1997, pp 4-34.

203. Speroff L, Do progestins attenuate estrogen's beneficial effects on the cardiovascular system? In Forte TM, editor, *Hormonal, Metabolic, and Cellular Influences on Cardiovascular Disease in Women,* Futura Publishing Company, Inc., New York, 1997, pp 303-24.

204. Speroff L, Postmenopausal hormone therapy into the 21st century, Int J Gynecol Obstet 59(Suppl 1):S3-S10, 1997.

205. Speroff L, Omodei U, Menopausa e Bilancio rischio/beneficio della terapia ormonale sostitutiva, Ginecologia E Ostetricisa Nella Pratica Clinica, V. 3, 1997, pp 4584.

206. Speroff L, Berga SL, Birge SJ, Henderson VW, Sherwin BB, Mood, cognition, and dementia: effects of postmenopausal hormone therapy, Contemporary OB/GYN, February, 1998, pp 4-25.

207. Speroff L, Archer DF, Avioli LV, Bradshaw KD, Moghissi KS, Your menopausal patient: individualizing management, Contemporary OB/GYN, June, 1998, pp 4-28.

208. Speroff L, A quarter century of contraception: remarkable advances, increasing success, Contemporary OB/GYN, May, 1998, pp 13-28.

209. Speroff L, Azziz R, Dunaif A, Giudice LC, Sobel BE, Diagnosis and management of polycystic ovary syndrome, Contemporary OB/GYN, July, 1998, pp 4-26.

210. Speroff L, Mircette, a novel oral contraceptive, supplement editor and introduction, Am J Obstet Gynecol 179:S1, 1998.

211. Speroff L, Oral contraceptives and arterial and venous thrombosis: a clinician's formulation, Am J Obstet Gynecol 179:S25-S36, 1998.

212. Speroff L, Bachmann GA, Kleerekoper M, Mishell DR Jr, Stampfer MJ, Sullivan JM, Postmenopausal hormone therapy: treatment choices for medical conditions, Contemporary OB/GYN, November, 1998, pp 4-26.

213. Speroff L, The Heart and Estrogen/progestin Replacement Study (HERS), Maturitas 31:9-14, 1998.

214. Speroff L, Archer DF, Cook CL, Shiferen JL, Shumaker SA, Advances in transdermal postmenopausal hormone therapy, Contemporary OB/GYN, January, 1999, pp 4-26.

215. Speroff L, Kronenberg F, Liu, JH, Taylor M, Facts and fallacies: 'natural' alternatives for menopause? Contemporary OB/GYN, February, 1999, pp 4-21.

216. Speroff L, Role of progesterone in normal breast physiology, J Reprod Fertil 44:172-79, 1999.

217. Bush TL, Speroff L, Stampfer MJ, Bachman GA, Hormone replacement therapy and breast cancer: is there a link? Medical Crossfire, Feburary, 1999, pp 28-36.

218. Speroff L, Oral contraceptives and thrombosis, in Coutinho EM, Spinola P, editors, *Reproductive Medicine, A Millennium Review, The Proceedings of the 10th World Congress on Human Reproduction,* The Parthenon Publishing Group, New York, 1999, pp 46-54.

219. Speroff L, The estrogens receptor: changing concepts. Clinical lessons from molecular biology, in Coutinho EM, Spinola P, editors, *Reproductive Medicine, A Millennium Review, The Proceedings of the 10th World Congress on Human Reproduction,* The Parthenon Publishing Group, New York, 1999, pp 155-161.

220. Speroff L, Postmenopausal hormone therapy and breast cancer, in Coutinho EM, Spinola P, editors, *Reproductive Medicine, A Millennium Review, The Proceedings of the 10th World Congress on Human Reproduction,* The Parthenon Publishing Group, New York, 1999, pp 255-264.

221. Speroff L, Baker VL, Cummings SR, Goldstein SR, Gass ML, Morrow M, Walsh BW, Wenger NK, Selective Estrogen Receptor Modulators: Emerging role in the clinical setting. Effects on the breast and uterine tissues, Contemporary OB/GYN, May, 1999.

222. Speroff L, Interpreting the HERS trial results: proceed with caution, Contemporary OB/GYN, May, 1999, pp 87-94.

223. Speroff L, Breast cancer and HRT. A clinician's perspective on the research data, Women Health Primary Care 2(Suppl 1):15-22, 1999.

224. Speroff L, Modern low-dose oral contraceptive are very safe, J Clin Endocrinol Metab 84:1823-25, 1999.

225. Speroff L, Baker VL, Cummings SR, Goldstein SR, Gass ML, Morrow M, Walsh BW, Wenger NK, Selective Estrogen Receptor Modulators: Emerging role in the clinical setting. Skeletal and coronary effects, Contemporary OB/GYN, July, 1999.

226. Speroff L, Women's healthcare in the 21st century, Maturitas 32:1-9, 1999.

227. Speroff L, Postmenopausal hormone therapy and the risk of breast cancer, Maturitas 32:123-29, 1999

228. Speroff L, Bush T, Clarkson TB, Collins P, Walsh B, Hormone therapy and heart health in postmenopausal women, Contemporary OB/GYN, November, 1999.

229. Speroff L, Women's health care in the 21st century, Audio-Digest, Vol 46, Issue 24, December 21, 1999.

230. Speroff L, The menopause: A signal for the future, in Lobo RA, editor, TREATMENT OF THE POSTMENOPAUSAL WOMAN, Raven Press, New York, 1999, pp 1-8.

231. Speroff L, Walsh BW, Taylor MM, Bachmann GA, Healthy menopause in the 21st century, Meetings on Demand CD ROM, Contemporary OB/GYN, 1999.

232. Speroff L, Dysfunctional uterine bleeding, in Ransom SB, editor, PRACTICAL STRATEGIES IN OBSTETRICS AND GYNECOLOGY, W. B. Saunders Company, Philadelphia, 1999, pp 560-69.

233. Speroff L, Creasman WT, Schwartz PE, Estrogen replacement in patients with cancer, ACOG Update, Vol 25, Issue 11, 2000.

234. Speroff L, Interventions for the control of symptoms, in Lobo R, Kelsey J, Marcus R, editors, MENOPAUSE: BIOLOGY AND PATHOBIOLOGY, Academic Press, 2000, pp 553-62.

235. Speroff L, Hindle WH, Kenemans P, Knopp RH, Richart RM, Taylor M, Global options for postmenopausal hormone therapy, Contemporary OB/GYN, January, 2000.

236. Speroff L, A clinician's response to the oral contraceptive thrombosis controversy, Hum Reprod Update 5:654-63, 2000.

237. Speroff L, It's time to stop using the word "replacement," Maturitias 34:1-3, 2000.

238. Speroff L, Postmenopausal estrogen-progestin therapy and breast cancer: a clinical response to epidemiological reports, Contemporary OB/GYN, March, 2000; and Climacteric 3:3-12, 2000.

239. Speroff L, Oral contraceptives and breast cancer risk: summary and application of data, Int J Fertil 45(Suppl 1):65-72, 2000.

240. Speroff L, A Clinical understanding of the estrogen receptor, in Creatsas G, Mastorakos G, Chrousos GP, editors, THE YOUNG WOMAN AT THE RISE OF THE 21ST CENTURY, Ann NY Acad Sci 900:26-39, 2000.

241. Speroff L, The perimenopausal transition, in Creatsas G, Mastorakos G, Chrousos GP, editors, THE YOUNG WOMAN AT THE RISE OF THE 21ST CENTURY, Ann NY Acad Sci 900:375-92, 2000.

242. Speroff L, Creasman WT, Schwartz PE, Estrogen replacement in patients with cancer, ACOG Update, May, 2000.

243. Speroff L, Oral contraceptives and carbohydrate metabolism, Dialogues in Contraception, Vol. 6, No. 4, Summer, 2000.

244. Speroff L, Postmenopausal hormone therapy and coronary heart disease: clinical implications of recent randomized trial results, Maturitas 35:91-97, 2000 and Contemporary OB/GYN, August, 2000.

245. Speroff L, Management of the perimenopausal transition, Contemporary OB/GYN, September 15, 2000.

246. Jensen JT, Speroff L, Health benefits of oral contraceptives, Obstet Gynecol Clinics No Am 27:705-21, 2000.

247. Speroff L, The estrogen receptor: changing concepts, Climacteric 3(Suppl 1):2-13, 2000.

248. Speroff L, Hormone replacement therapy: clarifying the picture, Hospital Practice 36:37-46, 2001

249. Speroff L, Postmenopausal hormone therapy and primary prevention of cardiovascular disease — Nurses' health study 20-year follow-up, Maturitas 38:221-224, 2001.

250. Speroff L, Postmenopausal estrogen therapy and ovarian cancer, Contemporary OB/GYN, May, 2001, pp 77-81.

251. Speroff L, Gallagher JC, Pinkerton JV, Raisz LG, Montgomery Rice V, Menopause management: the impact of low-dose HRT, Contemporary OB/GYN, Supplement, July, 2001.

252. Speroff L, Bachmann GA, Herrington DM, Simon JA, HRT: Putting the Latest Data into Practice, Patient Care, Supplement, October, 2001.

253. Speroff L, Inconsistency in epidemiologic findings on postmenopausal hormone therapy and breast cancer, Women's Health (Supplement), October, 2001.

254. Blackwood MM, Creasman WT, Speroff L, Postmenopausal hormone therapy: informed patients, shared decisions, Women's Health (Supplement), October, 2001

255. Speroff L, Hormone replacement and breast cancer. What are the connections? The Female Patient (Supplement), December, 2001, pp 6-12.

256. Speroff L, The meaning of mammographic breast density in users of postmenopausal hormone therapy, Maturitas, 41:171-175, 2002; Contemp OB/GYN June, 2002, pp. 111-118.

257. Speroff L, The perimenopause. Definitions, demography, and physiology, Obstet Gynecol Clin N Am 29:397-410, 2002.

258. Speroff L, A response to critics of long-term postmenopausal hormone therapy, Contemp OB/GYN July 2002, pp. 98-102.

259. Speroff L, The impact of the WHI on clinical practice, J Soc Gynecol Invest 9:251-253, 2002.

260. Speroff L, A clinician's medical judgment, Maturitas 44:11-18, 2003.

261. Speroff L, Gallagher JC, Rice VM, Lower-dose therapy: a new option in menopause management, Contemp OB/GYN May, 2003, pp. 4-19.

262. Speroff L, The WHI and breast cancer: what does it mean?, Menopausal Medicine 11:4-7, 2003.

263. Speroff L, Clarkson TB, Is tibolone a viable alternative to HT? Contemp OB/GYN August 2003, pp. 54-67.

264. Speroff L, Putting the WHI report on breast cancer in perspective, Contemp OB/GYN August 2003, pp. 68-76.

265. Speroff L, The million women study and breast cancer, Maturitas 46:1-6, 2003

266. Speroff L, WHI trial: it's time to be critical, Am J Obstet Gynecol 189:1-2, 2003.

267. Speroff L, HT: A Clinician Demurs, Sexuality Reproduction & Menopause 1:15-18, 2003.

268. Speroff L, Alternative therapies for postmenopausal women, in Studd J, ed., *The Management of the Menopause,* Third Edition, Parthenon Publishing Group, 2003, pp. 261-174.

269. Speroff L, The WHI estrogen-only arm is canceled, Maturitas 48:3-4, 2004.

270. Speroff L, What I've learned from the emotional and political response to the WHI, Contemporary OB/GYN, June, 2004, p. 104.

271. Speroff L, Postmenopausal hormone therapy and the risk of breast cancer. A clinician's view, Maturitas 49:51-57, 2004.

272. Speroff L, Postmenopausal hormone therapy and breast cancer. A clinician's message for patients, Endocrine 24:211-216, 2004.

273. Speroff L, Carlos Montezuma, M.D., A Yavapai American Hero, Prologue, The Quarterly Magazine of the National Archives and Records Administration, 36:38-47, 2004.

274. Speroff L, A clinician's review of the WHI-related literature, Int J Fertil Women's Med 49:252-267, 2004.

275. Speroff L, A clinician's response to the WHI, in Schneider HPG, Naftolin F, editors, *Climacteric Medicine. —Where Do We Go?*, Taylor & Francis, London and New York, 2005, pp. 104-109.

276. Speroff L, Hormone therapy: is it for me?, Female Health Today, 2005, pp 4-8.

277. Kaunitz AM, Speroff L, Contraception in the perimenopausal women, Dialogues in Contraception, 9:104, Spring, 2005.

278. Speroff L, Clinical appraisal of the Women's Health Initiative, J Obstet Gynaecol Res 31:80-93, 2005.

279. Speroff L, Postmenopausal hormone therapy and the risk of ovarian cancer: a review of the literature, Menopause Management January/February:23,23-28, 2005.

280. Speroff L, Bioidentical hormones, Menopause e-Consult, I:1-2, April, 2005..

281. Kenemans P, Speroff L, Tibolone: clinical recommendations and practical guidelines. A report of the International Tibolone Consensus Group, Maturitas 51:21-28, 2005.

282. Speroff L, Kenemans P, Burger HG, Practical guidelines for postmenopausal hormone therapy, Maturitas 51:4-7, 2005

283. Speroff L, Endometrial Cancer—Surprising Reports, Maturitas 51:329-333, 2005.

284. Speroff L, Clinical implications of hormone-induced breast density, Menopause Management 13:1-4, 2005.

285. Speroff L, Postmenopausal hormone therapy and cardiovascular disease. One view of the elephant, Menopause 12:357-358, 2005.

286. Speroff L, Hormone therapy. Safe and sensible or hazardous to your health? Women's Health Today, Fall 2005, pp 30-32.

287. Speroff L, Alternative therapies for postmenopausal women, Int J Fertil 50-:101-114, 2005.

288. Speroff L, Using aromatase inhibitors to treat breast cancer, Contemproary OB/GYN, February 1, 2006, pp. 60-66.

289. Speroff L, The WHI report on calcium and vitamin D supplementation: good news, not bad news, Menopause Management 15:24-26,39, 2006.

290. Stevenson JC, International Consensus Group on HRT and Regulatory Issues, HRT, Osteoporosis and Regulatory Authorities, Hum Reprod 21:1668-1671, 2006..

291. Hilliard P, Speroff L, . . . what about my headaches?, Contemporary OB/GYN, September 1, 2006, pp. 38-41.

292. Speroff L, Kaunitz AM, Contraception for the woman with medical problems, Dialogues in Contraception, Winter, 2006.

293. Speroff L, Premenopausal atherosclerosis. Setting the stage for later clinical events, Contemporary OB/GYN, March, 2007, pp. 84-89.

294. Speroff L, Clinical update on tibolone, Menopause Management, March/April (Supplement), 2007, pp. 32-34.

295. Speroff L, Evaluating the evidence for aromatase inhibitors to treat early breast cancer, Paitent Care Women's Health, April, 2007, pp. 7-11.

296. Speroff L, Transdermal versus oral postmenopausal therapy: is there a clinical difference? NWNP, Spring, 2007.

297. Speroff L, Gonads are the heart of the matter, Menopause 14:342-344, 2007.

298. Speroff L, What have we learned from the WHI? Contemporary OB/GYN, May, 2007, pp. 12-17.

299. Speroff L, Meta-analysis is to analysis like meta-physics is to physics, Contemporary OB/GYN, June, 2007, p. 116.

300. Speroff L, *Festschrift* for Peter Kenemans, Maturitas 57:1-2, 2007.

301. Mishell DR Jr, Speroff L, Polycystic ovary syndrome: management and contraception, Dialogues in Contraception, Spring, 2007.

302. Speroff L, Barnhart KT, Gonzalez J, The menopause: a signal for the future, in Lobo RA, editor, TREATMENT OF THE POSTMENOPAUSAL WOMAN. BASIC AND CLINICAL ASPECTS, 3rd edition, Academic Press, Burlington, MA, 2007, pp. 1-13.

303. Speroff L, Is the transdermal contraceptive associated with a greater risk of venous thrombosis than an oral contraceptive? Contemporary OB/GYN, December, 2007, pp. 50-53

304. Pinkerton JV, Archer DF, Lindsay R. Speroff L, Use of low-dose hormone therapy in menopause: changing perspectives, Contemporary OB/GYN, December, 2007.

305. Shulman LP, Speroff L, Contraception and cancer, Dialogues in Contraception, Vol. 12, Issue 1, www.cmeuniversity.com, Spring, 2008.

306. Speroff L, The strength of a man's intellect, Contemporary OB/GYN, May, 2008, pp. 91-92.

307. Speroff L, Should women stop hormone therapy before surgery? Contemporary OB/GYN, May, 2008, p. 64.

308. Speroff L, Mishell DR Jr, A commentary. The postpartum visit: it's time for a change in order to optimally initiate contraception, Contraception, in press.

July, 2008